ARCHIVES OF DISEASE IN CHILDHOOD.

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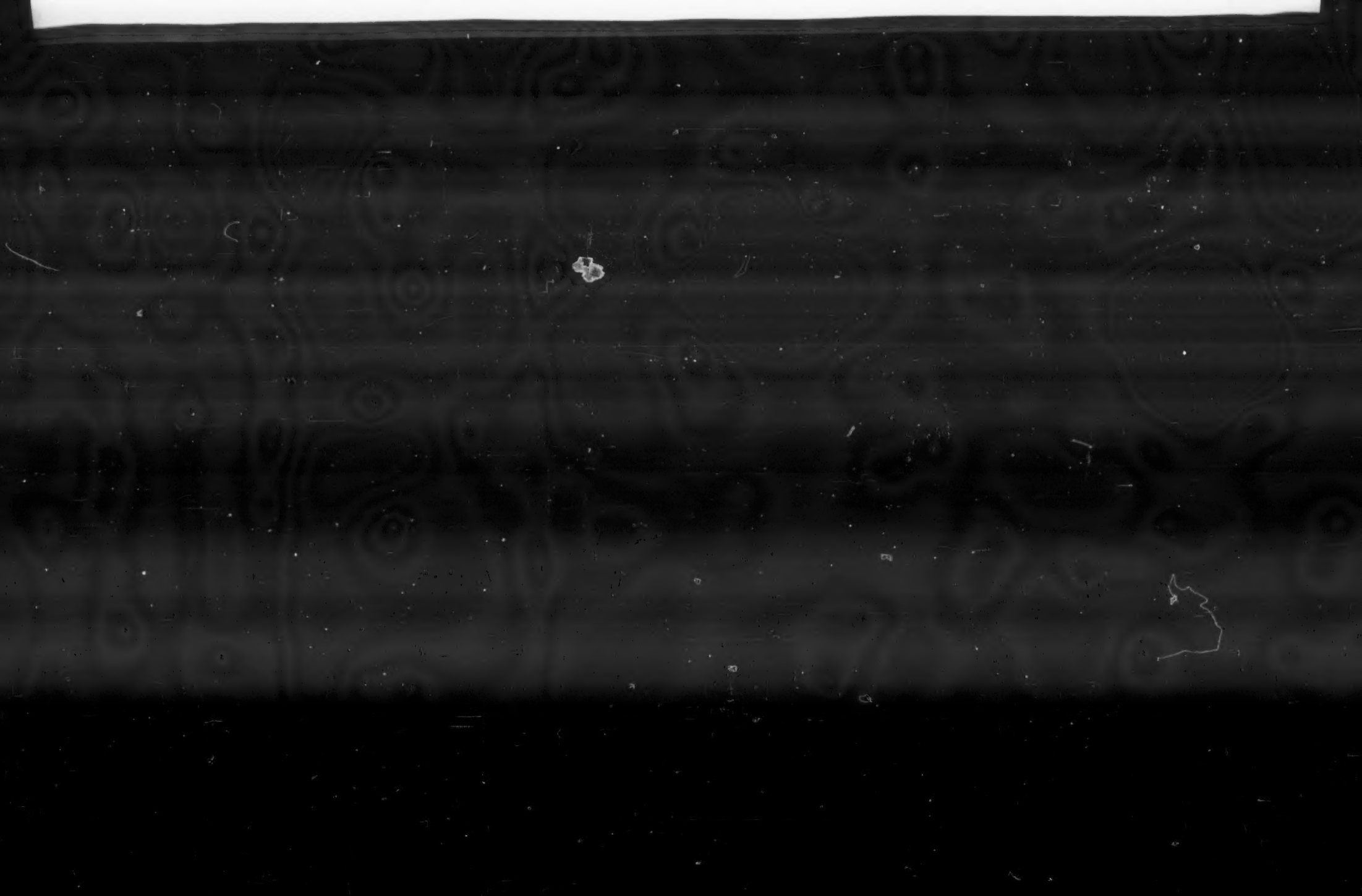

ARCHIVES OF DISEASE IN CHILDHOOD.

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INTRODUCTION

BY

SIR THOMAS BARLOW, Bt., M.D., F.R.S.

The study of children's diseases differs from the study of other specialties of medicine, because its association with general medicine is more intimate and continuous than is the case in other specialties. This applies all along the line, to research, to clinical observation, to teaching and to practical therapeutics. A fair case indeed could be made for treating this subject as an integral part of general medicine, but for convenience of reference it deserves a notable place amongst special branches.

In an important address given some years ago by Dr. Gee on the history of the study of children's diseases, the claim was made that the great landmarks in the subject had been discovered and expounded by general physicians rather than by specialists. But during the last decade such important steps have been achieved in bacteriology, biochemistry and in clinical observation likewise, that the soundness of Gee's dictum, so far as the present generation is concerned, may now be disputed.

What reasons can be urged for the publication of "Archives of Disease in Childhood" in this country?

(1) Because of the necessity that the *conclusions* obtained by various workers and scattered through various publications should be rendered available; (2) because there ought to be an opportunity for keen workers in the many departments of children's diseases to publish and submit for criticism and verification their varied observations and experiments; and (3) because of the need to set forth in concrete and detailed form the results of new discoveries in diagnosis and treatment with a view to their employment in practice for the public good.

When we reflect on the generalisation which applies to the symptomatology of disease in child life and on the responsiveness of the child's nervous system we must deprecate any marked dichotomy of specialism in so far as the *organs* of the child are concerned. A more desirable classification in spheres of labour would seem to be based on the *different periods of child life.*

Pre-natal life; infancy reckoned from birth to the age of two years; early childhood, from two years to five years of

age; late childhood, from five years to puberty, would seem to be a fair division.

Of these the pre-natal period in many ways seems the most important and far-reaching; obscure and limited as it is, some valuable additions have lately been made to our knowledge concerning it. The nutrition of the mother, considered exclusively as it affects that of the fœtus, may be very important indeed. It has been denied that there is any true fœtal rickets apart from osteogenesis imperfecta and achondroplasia. These two categories as well as early *fragilitas ossium* may be classified with developmental vagaries and associated with congenital malformations. But does true rickets sometimes begin in the *fœtal period*? It is noteworthy that in families in which several members are successively rickety the early children are least so, and the later children are increasingly so. This suggests that the mother's gradual failure in nutrition during successive pregnancies may play some part in the ætiology. The date at which the earliest tangible evidence of rickets becomes manifest may throw light on this question.

The trend of clinical observation and of therapeutic experience seems after all to point to the rickets with which we are concerned as mainly a post-natal and predominantly a food disease. The experiments on puppies performed by Dr. Mellanby would seem to place rickets amongst the "deficiency" diseases, the deficiency being in protein and absorbable fat and probably therewith the activating fat soluble vitamin A. The most efficient of all foods in the prevention of rickets in the infant period is admittedly mother's milk, but fresh cow's milk, cream, butter, suet, egg, dripping and animal fats have all to be reckoned with as useful and efficient substitutes under certain limitations. Animal fats are definitely superior to vegetable fats, butter being far better than vegetable margarine and cod liver oil than olive oil. The premature addition of carbohydrates to the infant's food would appear also to be a definite factor in this disease, and the dilution of cow's milk to which Dr. Still has drawn special attention, has probably been more responsible than we were at one time prepared to admit. Budin's contention with regard to infant feeding in favour of *undiluted cow's milk*—albeit in quite small quantities at a time and at more frequent intervals than the arbitrary "four hourly feeds"—demands careful reconsideration by English physicians.

Condensed milk, both sweetened and unsweetened, has been definitely condemned as an undoubted factor of rickets. Dried milk, on the other hand, appears to have secured a place as one

of the fairly good substitutes in infant feeding, though further experience is desirable, especially in relation to infantile scurvy.

The cases of entirely breast fed infants who contract rickets would probably repay further investigation. Dr. Still attributes the rickety outcome in these cases to the extreme thinness of the mother's milk.

We now agree that Parrot's cranial bosses are truly rickety periostoses, though it is granted that the co-existence of the congenital syphilitic infection may render these and other rickety bone changes decidedly more pronounced. In the study of the pathology of rickets considerable attention has rightly been given to the changes in the epiphysial junction areas; but the rôle of the periosteum in the membrane-formed bones is equally important and, indeed, also the rôle of the periosteum of the shafts of the long bone. Hereditary syphilis is not the only co-operant form of lowered nutrition in the causation of rickets. Cretinism often shows marked combinations with rickety characters. Infantile scurvy is often grafted on rickets, and the occurrence of the complex of scurvy-rickets has been responsible for the delay in the accurate recognition of true scorbutic signs. Intercurrent acute specific illnesses, bronchitis and chronic gastro-enteritis, often cause aggravations and relapses of rickets.

Other important factors of this disease, namely, lack of sunlight and fresh air, and the sum total of what we describe as the results of overcrowding, have been long acknowledged, but the experience of Dr. Hess and his colleagues, and the post-war work of Miss Chick with the Vienna poor children, have given definiteness and emphasis to these factors. The remarkable therapeutic experiences of Dr. Hess and others, showing that the radiation of the mercury vapour quartz lamp can to some extent substitute direct sunlight in the cure of rickets, will probably have important results on practice. The recognition of the effect of ultra violet radiation in activating green vegetables and milk may likewise prove helpful.

With respect to infantile scurvy, in Great Britain the occurrence of this disease in a baby entirely breast fed is extremely rare, but there are records of foreign cases in which this occurrence seems to be undeniable. As in the prevention of rickets, it is very desirable that the pregnant mother should be able to secure for herself milk from cows fed on fresh grass and living largely in the open rather than stall fed, and that the food of the mother should also include a plentiful supply of fresh vegetables.

With respect to maternal syphilis, if there is the least reason to believe that there has been any former infection, a

Wassermann test ought certainly to be made, and if positive ought to be followed by definite treatment. The results of inoculation of the mother, with one of the arseno-benzol preparations given regularly from the earliest period of pregnancy up to the time of delivery, have proved strikingly beneficial by way of immunisation to the infant.

When artificial feeding has to be adopted either wholly or in part, the question of boiling cow's milk requires decision. Repeated boiling, like repeated sterilisation, is certainly wrong. When infantile scurvy has become manifest in a given case any boiling whatever probably reduces the anti-scorbutic efficiency of milk, and unboiled milk in small quantities can be tolerated often with remarkable success. But a single boiling, just before the feed is given, is generally safe and wise. With regard to the anti-scorbutic additions, potato roasted in the skin and the mealy part of the potato scraped and sieved into milk, has proved satisfactory as the initial measure. Orange juice or grape juice are useful adjuncts, and good meat gravy, or home-made meat juice, are likewise of service as additions to the milk. Boiled yolk of egg is a useful standby. With regard to proprietary foods and their relation to infantile scurvy, there is little new to be said, except that they retain their supremacy as amongst the chief offenders in the causation of the disease.

Amongst the practical problems of the period of infancy (that is from birth to two years of age) artificial infant feeding is surely the most insistent and most difficult to carry through on anything like sound lines. None of the alimentary problems has commanded more zeal and patient investigation than what we have provisionally agreed to describe as congenital hypertrophy of the pylorus or otherwise as hypertrophic stenosis of the pylorus. Dr. Cameron has indeed pointed out in his admirable Lumleian lectures that neither of these names is satisfactory or indeed strictly correct. Further knowledge is needed in order to define in any accurate descriptive title the true notes of the disease.

No doubt Hurst's original work some years ago, on the mechanism of the alimentary canal and his contention for what he has called Achalasia (which has been defined as the absence of relaxation) gave a direction to enquiry, although he was not specifically concerned with this disease.

The two doctrines held as to the pathology of hypertrophic stenosis of the pylorus may be defined as (1) that of Hirschsprung supported by Cautley, according to which there is a primary hypertrophy of the pylorus; (2) that of John Thomson, according to which there is inco-ordination of the muscles

concerned in contraction and consequent propulsion of the food content and the relaxation beyond, which permits of the initial propulsion becoming operative; in other words, there is disharmony and inco-ordination between the stomach wall and the pylorus. With regard to Hirschsprung's and Cautley's contention it may be said that hypertrophy independently of antecedent obstruction or resistance is not in harmony with what we know of pathology in other regions. With regard to Thomson's ingenious hypothesis (which it may be mentioned he has also applied to the explanation of hypertrophic dilatation of the colon), it may be observed that it carries the difficulty back to the enquiry what then is the cause of this disharmony and inco-ordination and how is it brought about? But although the pathology of this disease is still doubtful we owe a great debt to the British school for the elucidation of its natural history and for the important fact that we no longer regard it as a hopeless and insoluble mystery, but as a morbid entity which is capable in very many instances of complete restoration. Dr. Nicoll, of Glasgow, had the great merit of introducing in his case in 1900 Loreta's operation of dilatation of the pylorus which was successful; according to Dr. Thomson this patient made such a good recovery that eighteen years afterwards he was passed as a sound life for the Army.

Thomson, Still, Cameron and Cautley, with the invaluable help of their surgical colleagues, Stiles, Burghard and Dent, have added a real chapter to medicine, nor can we forget the important contributions of Holt, Hirschsprung, Dufour and Fredet, and on the surgical side the brilliant contributions of Rammstedt.

It is most important, and indeed invaluable, that the indefatigable workers at this disease have established the two clinical features which are imperative in the diagnosis, namely, (1) the demonstration of a visible stomach peristalsis, and (2) the palpation of a definite resisting tumour due to the pylorus which is in a state of spasm. Grasping these fundamental conditions, what are the chief indications for medical treatment of an early and moderate case of this disease? (1) The maintenance of breast feeding, maternal if possible, or that of the wet-nurse; (2) small feeds and, if necessary, at shorter intervals than normal; (3) the employment of stomach lavage once or twice daily, but guided as to frequency by the varying incidence of stomach dilatation and food delay. In a fair number of cases these methods have proved successful. The real trouble being caused by what is equivalent to a mechanical difficulty, alteration in the composition of the feed is not indicated, and

it is noteworthy that in the typical favourable case signs of food toxæmia in the early stage are conspicuously absent. If under these methods there is no amelioration, and the vomiting increases in severity with rapid wasting and threatening of toxæmia, then surgical aid should be invoked. Also, if from the onset the case is acute, primary surgical operation would appear on the whole to give the best chance.

Some of the surgical procedures which were employed in the early cases, for example gastroenterostomy, have now been negatived, and there remain two from which excellent results have been obtained, (1) Laparotomy, followed by Loreta's method of dilatation of the pylorus (Burghard and Stiles); (2) Laparotomy followed by longitudinal incision of the peritoneum over the pylorus and of the muscular fibres down to but *not through* the mucous membrane, so that no opening is made into the stomach (Rammstedt).

Rammstedt's operation seems at present to command most confidence, but this is a matter in which the personal equation and experience of the operator must count for a great deal.

There is not adequate space in this introduction to refer to many other important additions which have been made during the last decade to the pædiatric outlook, both medical and surgical. The juvenile type of acute and sub-acute rheumatism requires a chapter of its own, and supplies in fact a fuller and certainly more interesting survey than the ordinary rheumatic fever attack of the adult. This is one of the cases in which the study of children's diseases contributes illumination to general medicine. The work of Poynton and Payne challenges candid re-consideration. What valid objections can be raised to their technique and to the soundness of their general contentions? The treatment of the convalescent period of acute and sub-acute rheumatism in the child and the precautions to be taken regarding the insidious incidence and increase of endocarditis merit patient enquiry and therapeutic experiment.

Great progress has been made in the orthopædic surgery of the deformities left by poliomyelitis. The subject of immunisation which began long ago with diphtheria, has made bold strides and has a great future. The recent work associated with the names of Schiff and Dick will at once occur to the modern reader.

The fields indeed are white unto harvest; the husbandmen are ready and skilful; the workers of bygone days hand on to them the sickle and wish them good luck and God speed. "He that soweth and he that reapeth shall rejoice together."

Medical and Chirurgical
Faculty of Maryland

HEPATIC CIRRHOSIS IN CHILDREN,
with special reference to the Biliary Forms.

BY

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The occurrence in hospital within a comparatively short space of time of four unusual examples of cirrhosis of the liver in young children has led us to make this communication.

Disorders of the liver in childhood have in recent years not attracted much attention in this country, and we feel that the mere ventilation of the subject, though we may have little new to add, may serve a useful purpose.

It is possible that others besides ourselves have been inclined to be guided in their views upon cirrhosis of the liver by a recollection of cases of alcoholic cirrhosis in the adult, and to recall such symptoms as chronic gastritis and vomiting, hæmatemesis, ascites, jaundice, pruritus, dilated capillaries on the cheeks, the caput medusæ, and concomitant results of the particular cause such as sleeplessness, wasting, loss of memory, and tremor. Again it is possible that admitting the rarity of alcohol as a causal factor in the child we incline over much to a syphilitic origin. It is, we believe, a more illuminating, though certainly a difficult undertaking, to discard entirely our views upon cirrhosis of the liver in adults and to approach the problem in the child from the clinical and pathological features at that age.

Among the symptoms that we associate with cirrhosis of the liver in childhood there are many of those which we have already mentioned in referring to alcoholic cirrhosis. Epistaxis may be frequent, and telangiectases are often present, so that the face may present at a glance an aspect similar to that of chronic alcoholism. Ascites, however, and dilatation of the superficial abdominal veins, are often absent, and more remarkable still there may be no digestive disturbance. Special features related to childhood are infantilism, and a familial occurrence of the disease, which in its frequency is very striking.

In adults suffering from chronic cirrhosis there may occur a sudden intensification of the jaundice with fever, nervous symptoms and death in coma, and microscopy shows an acute destruction of liver cells. In childhood, also, such a development may supervene and be a cause of death from acute red atrophy. In these instances we seem to be able to trace a correlation between the urgent symptoms and the destruction of the liver cells. Here in child and adult the picture is identical. In children, however, more than in adults, this exacerbation of damage to the hepatic cells may assume a subacute form, possibly owing to the greater reparative powers possessed by the liver in the young.

The pathogenesis of hepatic cirrhosis in children is more often obscure than it is in adults. As to its frequency in childhood, some idea of the rate of incidence may be gained from the figures given by Graham Forbes.[1] He collected forty cases out of a total of five thousand, five hundred autopsies at the Children's Hospital, Great Ormond Street, which covered a period of forty-five years.

DESCRIPTION OF CASES.

Case I.

Katherine H., aged eight years, had a history, covering a period of nine months, of loss of appetite, listlessness, chilliness, sleepless nights, pains across the stomach, and of becoming yellow. There was no diarrhœa, vomiting, or epistaxis. The only previous illness had been whooping cough, but she was stated not to have been in really good health for the last three years. Both parents were healthy, but several of the mother's relatives had suffered from tuberculosis. There were four other children living besides the patient, these being younger than herself, but none of these had ever been jaundiced. In two young sisters, however, the liver was easily palpable.

On admission to hospital the patient was considerably jaundiced, had dilated veins on the chest and abdomen and a few telangiectases on both cheeks. The abdomen was rather large and doughy, the lower edge of the liver extending two finger-breadths below the costal margin. The liver was hard in consistency and the spleen was just palpable. There was no ascites. Bile pigments were not found in the urine and the fæces were quite well coloured.

Slight enlargement of the cervical glands was present. The tonsils had been enucleated previously. No evidence of disease of the heart, lungs or nervous system was obtained. Examination of sputum for tubercle bacilli was negative.

Investigations:

Van den Bergh's test gave both positive biphasic and indirect reactions (suggestive of an incomplete obstruction of the bile passages, with a fair degree of liver damage). The blood fragility test gave a normal result. Erythrocytes amounted to 4,320,000; leucocytes 5,620 per cubic millimetre, of which 46% were polymorphs and 49% lymphocytes. In both the patient and her mother the Wassermann reaction of the blood was negative. The patient gave a positive von Pirquet reaction to human tuberculin. A subcutaneous injection of Koch's O.T. 0·001 cc. produced both a general and a local reaction, and both the liver and spleen subsequently became larger.

Progress:

On discharge from hospital the jaundice had entirely disappeared, but both the liver and the spleen were still easily palpable. Within the next twelve months she had two attacks of erysipelas, and several attacks of jaundice with hæmatemesis and epistaxis. When last seen, at a recent date, there was no jaundice, the liver was palpable, but the spleen could not be felt. She appeared to be in fairly good health.

Cases II. and III.

These patients, a brother and sister, were of an even more unusual type. That the disorder was of congenital origin was indicated by the fact that the abdomen in each case was enlarged at birth. One of the most puzzling features, however, was the absence of jaundice except as a transient complication of an intercurrent infection.

Both children, A. B., seven years and four months, and O. B., three years and two months, were born at full term and in normal labour. In both it was noticed at birth that the abdomen was abnormally large. The parents were both healthy and had never been jaundiced. There was a third child, an infant of five months, which was

Fig 1.—Albert and Olive B.

examined also, in whom neither the liver nor the spleen was increased in size. A history of alcoholism in the parents could be excluded. The Wassermann reactions of the blood of the parents and of the two affected children were negative.

A. B. was first admitted to hospital in May, 1920, when three years and two months old. At this time a history was obtained that he had suffered from epistaxis, but had never been jaundiced. He had an attack of pneumonia a few months previously. The liver was found to extend below the umbilical level, its upper limit being at the fifth rib in the mammary line. In circumference the abdomen at its widest girth measured 25 inches. The spleen and kidneys were not palpable. Numerous dilated capillaries were present on both cheeks. Icterus and ascites were absent. No rise of temperature occurred and the stools were of a normal colour. The urine presented no peculiarities. A blood count showed R.B.C. 4,900,000, and W.B.C. 10,600; polymorpho-nuclears 50%.

In March, 1921, the child was re-admitted with a history of having been suddenly overcome, four weeks previously, with sickness, which lasted for five hours. Three days from the onset of the sickness he became feverish, drowsy, constipated, and had headache and abdominal pains. Four days later he vomited blood, his nose bled, and jaundice appeared for the first time. The jaundice deepened, and there were two further attacks of epistaxis, one being brought on by a fit of coughing. On examination he was found to be deeply jaundiced and the lower edge of the liver reached down to the right iliac fossa and the spleen was definitely enlarged. In circumference the abdomen measured $26\frac{3}{4}$ inches. In little more than a month from its onset the jaundice had entirely disappeared. The child then developed scarlet fever and was transferred to the fever hospital.

When next re-admitted to hospital in June, 1924, when seven years and four months old, the liver was found to extend downwards only as far as the umbilicus; the spleen and kidneys were not palpable. The abdominal girth was $25\frac{1}{4}$ inches. On palpation the liver was hard but no irregularity of its surface could be detected. Jaundice and ascites were absent, and the stools and urine were those of a normal healthy child. Epistaxis did not occur. No prominence of the superficial abdominal veins was observed. Telangiectases were present on the face as mentioned already. There was no clubbing of the fingers. A blood count showed the erythrocytes to number 4,240,000, leucocytes 22,540, of which 51% were polymorpho-nuclear cells. The child's height was 38 inches, the normal average for his age being 47 inches. His mother declared that he had developed normally up to the age of four years, but since then had not appeared to grow at all. Skiagrams revealed no bony deformities, but showed a delay in the ossification of the carpus. It was also thought that the splenic and renal shadows were larger than normal.

O. B., the sister of the last patient, was first examined at the age of three years and two months. She had previously had measles, whooping cough, and an attack of tonsilitis, which was complicated by jaundice, lasting only a few days. The mother stated that the child's stools had always been of a natural colour, and there was no history of epistaxis.

In appearance the child was small and fat, and the abdomen was strikingly prominent. In circumference it measured $22\frac{1}{2}$ inches. She was roughly $4\frac{1}{2}$ inches beneath the average height for her age. Numerous telangiectases were present upon the cheeks, but there was no jaundice or ascites. The superficial abdominal veins were not visible. The lower edge of the liver reached the level of the umbilicus, its upper limits being normal. In consistency this organ was firm and hard, but no nodules could be detected. The spleen was thought to be just palpable; the kidneys could not be felt. No trace of bile was discovered in the urine, and the stools and temperature were normal. Examination of the blood showed the R.B.C. 4,500,000 per c.mm. and W.B.C. 19,688, of which the percentages of polymorpho-nuclears and lymphocytes were equal. Skiagrams showed variations from the normal very similar to those found in the brother, namely, a delay in ossification of the carpus and an increase in the size of the splenic and renal shadows. There was no clubbing of the fingers.

Various tests of the state of the blood and the efficiency of the liver were carried out in the biochemical laboratory of the hospital by Dr. Harrison. The blood fragility, blood diastase and cholesterol were all within normal limits in both cases. The blood sugar, however, was slightly below the average, being 0·053 and 0·056 respectively. There was a very definite lipæmia of the blood of each patient, as seen in the separated serum. Van den Bergh's and the lævulose tests both gave normal results. There were, therefore, no definite signs of inefficiency of the hepatic functions. It must be observed, however, that an absence of abnormality in the results of the various hepatic efficiency tests is in no way conclusive that the liver is sound. To obtain results indicative of an impaired efficiency, as is known from experiments upon animals, a very large proportion of the whole hepatic

substance must be in a state of disorder. It is probable, therefore, that the two children were examined during a quiescent stage of the disease, and that they might give positive results of impaired efficiency to the tests on other occasions. In this connection it is of interest that icterus had appeared temporarily in each child as a complication of some intercurrent febrile disturbance. This suggests that the margin of efficiency of the already damaged liver was sufficient for ordinary purposes, but inadequate to deal with a toxæmia superadded from whatsoever cause.

Reviewing these three cases, it is to be noted that in one the condition was first noticed at the age of eight years, attention being drawn to it by the presence of jaundice. The jaundice was intermittent, disappearing entirely from time to time. Such symptoms as telangiectases on the face, dilatation of the superficial abdominal veins, epistaxis and hæmatemesis were all present. Ascites, however, did not occur. The child appeared to be the only affected member of a numerous family.

In the other two cases the condition was both familial and congenital. The familial occurrence of hepatic cirrhosis and even a history of jaundice in one or other parent has often been recorded. In the present instance, however, although both parents were apparently exempt, it was stated that an uncle of the father, and two children of one of the father's cousins, had had enlarged abdomens and were stunted in growth, though otherwise healthy. It has not been possible to verify these statements.

Both these children showed distinct signs of infantilism, particularly in their stature; both had telangiectases on the face, and both had a history of epistaxis. Other symptoms common to hepatic cirrhosis were absent, such as ascites, dilatation of the superficial abdominal veins, and the degree and duration of jaundice in either case were remarkably slight.

The amount of splenic enlargement in all three cases was a minor feature in the clinical picture, and moreover was not of a permanent character.

The possibility of an infection invading the system and proving a factor in the development of cirrhosis is suggested by the following case.

Case IV.

A female, aged five years, was admitted on March 6th, 1925, with a history of jaundice of eight weeks' duration, with headache and grey motions.

The three children of this family had developed jaundice after "colds" within a week of one another. In each case the urine became high coloured and the motions pale, and all complained of headache.

The eldest, a boy aged nine years, recovered in three days; the youngest, a girl aged four, in a week; the middle one, the patient, appeared to have recovered after three weeks but then relapsed.

Their mother gave no history of previous attacks in the family, but a maternal uncle and aunt had suffered from jaundice when young. The three children were examined. The two that had recovered showed a slight icteric tinge of the sclerotics, and in both the liver, but not the spleen, was felt below the costal arch. The fragility of the blood cells was normal. Both showed some pallor but otherwise were healthy.

The child in hospital was well nourished but considerably jaundiced. There was no headache, pain or vomiting; the temperature was raised (100 F.). The liver extended three fingers breadth below the costal arch and was firm and smooth. The tip of the spleen could be just felt. The stools were light in colour, and the tests for bile in the urine were positive. Van den Bergh's test was positive, biphasic and indirect. The fragility of the red cells was diminished and the R.B.C. numbered 4,800,000 per c.mm., W.B.C. 9,000, the differential count giving polymorpho-nuclears 37%, small mononuclears 51%, large 9·5%, eosinophils 2%. After a few days the jaundice lessened, and though the stools were pale, bile was not again demonstrated in the urine.

Three weeks after admission the temperature, which had never been normal, began to rise, and on the twenty-eighth day reached 104 F., but the child, though listless, had no pain and did not seem ill. Both liver and spleen now commenced to enlarge, particularly the spleen, which, at the end of the month, reached nearly to the umbilicus. Neither organ was tender and there was no enlargement of the lymphatic glands. The urine, though darker, did not contain bile; the motions were, as before, pale in colour.

The enlargement of the spleen continued until it reached four inches below the costal margin, and the liver then extended below the level of the umbilicus. The wave of fever then slowly declined, and with this the liver and spleen, the latter particularly, began to diminish in size. The child herself looked better and gained in weight. By May the liver had shrunk to midway between the right costal margin and the umbilicus, and the spleen could only just be felt projecting below the left arch. The child still showed a yellow tinge in the conjunctiva and skin, and developed a peculiar rash, lichenoid in type, during this stage of recovery.

Prior to advancing any views as to the causation, congenital or acquired, or to the type of cirrhosis presented by these cases, the moment appears opportune to give a brief description of the various forms of hepatic cirrhosis, which may be met with in childhood.

Types of Hepatic Cirrhosis.

1. Multilobular (portal, "hobnail" or "alcoholic").
2. Syphilitic (pericellular).
3. Type associated with Wilson's disease (progressive lenticular degeneration).
4. Type associated with Icterus Gravis Neonatorum.
5. Hepatic cirrhosis in Banti's disease.
6. Type sometimes found in combination with "red atrophy" of the liver.
7. The Biliary Cirrhoses, including hypertrophic biliary cirrhosis (Hanot), congenital cirrhosis, with or without obliteration of the bile ducts, and obstructive biliary cirrhosis.

Relative Incidence.

It must be stated at the outset that the various forms are not given in order of the frequency of their occurrence. Some idea of their rate of incidence can be gained from the following figures which are taken from the postmortem records of the Children's Hospital, Great Ormond Street, covering the period from January, 1910, up to June, 1925. There were twenty-two cases of congenital biliary cirrhosis. Obliteration of the larger bile ducts was present in fifteen of these, while in the other seven the ducts were patent. The duration of life in both types did not exceed six months, the majority succumbing in the first few weeks, except in two cases without obliteration of the bile ducts, which lived just over a year. It is worth mentioning in connection with the group of congenital biliary cirrhoses that other congenital abnormalities were discovered in three instances. A congenital cardiac lesion, together with Mongolism on the one hand and deformity of the feet on the other, was present in two cases with obliteration of the bile ducts, and a patent ductus arteriosus was found in one case in which the bile ducts were not obliterated. Nineteen cases of syphilitic cirrhosis came to autopsy, and in one only were gummata of the liver found. All died below the age of eight months. A Wassermann test was performed in all except four and found to be positive. In the four cases just mentioned the family history and other signs of syphilis, besides the condition of the liver, confirmed the diagnosis. Of the portal or hobnail variety there were only three examples, two being nine, and the third three, years old. The types found in combination with splenic anæmia (Banti's disease), and "red atrophy" of the liver numbered one each. Obstructive biliary cirrhosis was present in two cases. There were no examples of icterus gravis neonatorum, nor of the cirrhosis associated with Wilson's disease.

1. *Portal or Multilobular Cirrhosis.*

True cases of portal or multilobular cirrhosis are much less common in children than those of the biliary type. Clinically the jaundice is intermittent and seldom deep, ascites usually makes its appearance and there is dilatation of the superficial abdominal veins. The tendency of the liver to become small by contraction of the fibrous tissues is much less noticeable in children than it is in adults with the same type of cirrhosis. Facial telangiectases, epistaxis and hæmatemesis occur. These latter symptoms, however, are common to nearly all the different forms of cirrhosis. It is seldom that any definite factor can be unquestionably accepted as the cause of the disease, but it is generally held that the exciting agents are conveyed to the liver by way of the portal tributaries and possibly by the splenic vein.

As examples, the cases recorded by Jollye[2] of a brother and sister, eleven and ten years of age, conform most closely to the "alcoholic" type. These children had been in the habit of drinking frequently small quantities of vinegar. Neither child was jaundiced, and the liver and spleen were not palpable. At the autopsy, permitted on one of the children, the liver was found to be granular and yellowish. Histologically the cirrhosis was definitely multilobular in distribution.

Out of the cases collected from the hospital records the following (one of Sir Archibald Garrod's) is a good example of multilobular cirrhosis where no predisposing cause can be traced in the previous history of the patient.

It is that of a girl of nine years, who developed jaundice, ascites and hydrothorax. At autopsy the liver was found to be much reduced in size, very rough and nodular, and with adhesions to the parietal peritoneum. During life there was no evidence of enlarged abdominal veins, but at the section large vessels were seen communicating between the right kidney, suprarenal and diaphragm, also between the diaphragm and the right pleura. The pancreas was very firm, the spleen large and congested. Old caseating glands were present in the mesenteric glands.

Pathologically, in a typical case the liver is usually enlarged, rather than reduced in size, coarsely nodular, pale and mottled, and shows on

FIG. 2.
Photograph of liver of Sir Archibald Garrod's case showing "hobnail" type of cirrhosis.

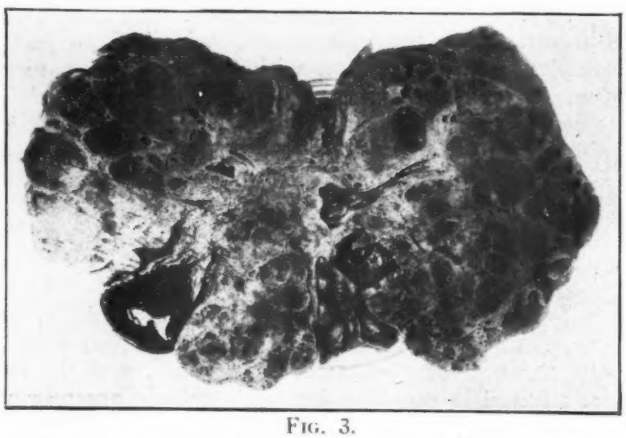

FIG. 3.
Liver from the same case as in Fig. 2, the cut-surface showing multilobular distribution of fibrosis.

section a multilobular distribution of the fibrosis. It is inaccurate, however, to suppose that all cases of the portal type show a multilobular cirrhosis, as not infrequently the fibrosis may be chiefly monolobular or mixed. In his Lumleian lecture of 1900, Cheadle,[3] in discussing adult alcoholic cirrhosis, stated that there was no question that a fine fibrosis, monolobular or intralobular in arrangement might occur in conjunction with hypertrophy of the liver. This variability in the distribution of the fibrous overgrowth occurs also in cirrhosis of the biliary type. Of greater importance, in distinguishing the two forms, is the presence of bile casts in the intrahepatic ducts and between the columns of liver cells, and of stippling of the liver cells with bile granules, which is a feature of the biliary form of cirrhosis. In portal cirrhosis the presence of pigment in the cells and bile casts is not seen unless jaundice has been definitely present at the close of the illness. Compression of the intrahepatic branches of the portal vein is more evident in the portal type of cirrhosis than in any other, which may be accounted for by the entry of the exciting poisons *via* the portal system.

2. *Syphilitic Cirrhosis.*

Syphilitic cirrhosis, in most cases, is readily distinguishable histologically by its pericellular distribution. The virus is conveyed to the liver from the placental blood by the umbilical vein. Jaundice is almost always present in this form, but in degree may be no more than a slight pigmentation of the skin. Ascites and dilatation of the superficial abdominal veins are frequently present.

As a typical case the following instance will serve :—

A female infant of four weeks was admitted to hospital with vomiting and progressive enlargement of the abdomen. A slight icteric tint of the skin had been noticed from birth. Ascites was present and the superficial veins of the abdomen were dilated. The liver was firm and easily palpable, and the spleen could also be felt. Other symptoms included snuffles, excoriations about the mouth, a papular eruption on the forehead, and one or two blisters on the palms of the hands and soles of the feet. The Wassermann reaction of the blood was strongly positive. She was the third child; the first, aged four and a-half, was alive and well; the second, born prematurely, died jaundiced a few weeks after birth.

Pathologically, in congenital syphilitic cirrhosis the liver is usually found to be enlarged, firm and smooth or finely granular, and of a dark colour, sometimes slate-blue. The cirrhosis is brought about by a small celled infiltration, which spreads indiscriminately throughout the organ. The cells are considered to arise from a proliferation of the connective tissue cells and of the endothelium of the intralobular capillaries and lymphatics (Allbutt and Rolleston). The fibrous tissue which is formed is both intralobular and pericellular. Obliterative changes of the hepatic artery are very rarely found. An apparent increase of the small bile ducts is sometimes present. Spirochaetes in large numbers may be demonstrated by suitable methods of staining.

3. *Cirrhosis associated with Progressive Lenticular Degeneration (Wilson's Disease).*

In these cases there is rarely any indication during life of hepatic disorder, but in three described by Wilson, attacks of jaundice, œdema of the legs and ascites occurred before the onset of the nervous symptoms. Tests of hepatic function, in suspected cases, have failed to reveal a morbid state of the liver.

Clinically, the essential features of the disease are related to the nervous system. Wilson described the disease as being " characterised predominantly

by bilateral degeneration of the lenticular substance," and considered that there was evidence of a toxic origin, the toxins possibly being elaborated in the liver.

A feature of great importance, from the point of view especially of the hepatic changes, is that the disease may be familial. In his original paper in *Brain*, 1912,[4] Wilson found the average age of onset to be fifteen years. The youngest of the cases he recorded was ten. In a case of one of us, published in full in *Brain*,[5] the onset was in the fourteenth year. The liver was small, tough and nodular, and presented the usual appearance of a multilobular cirrhosis. During life, however, no symptoms of hepatic disorder were present, and the liver was not palpable.

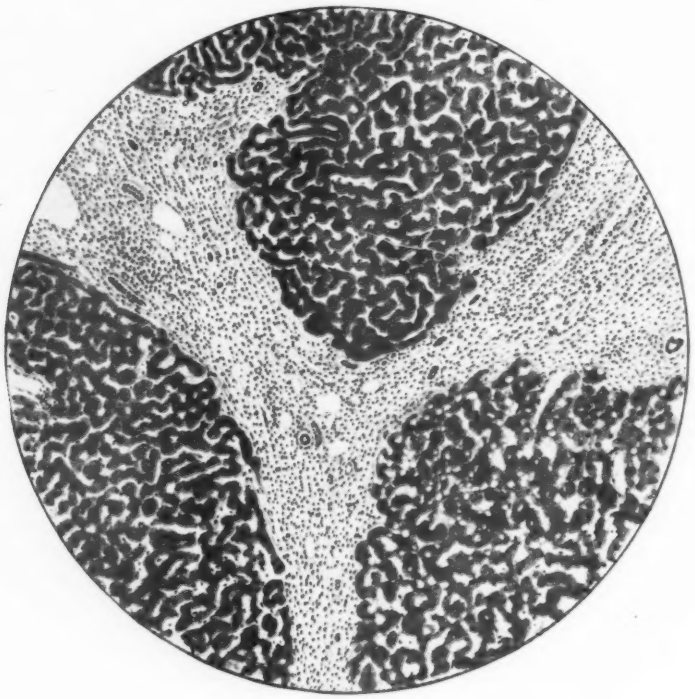

FIG. 5.

(X60) Section of liver from case of Progressive Lenticular Degeneration, showing coarse multilobular cirrhosis with very little damage to hepatic cells.

Here the type of cirrhosis is mainly multilobular. The liver is usually coarsely nodular and of a pale colour. There is considerable thickening of the portal tracts, but the portal vessels show little alteration. The bile canaliculi appear increased in number, but without any evidence of obliteration. In some nodules the hepatic cells appear fairly normal, in others necrotic.

4. *Icterus Gravis Neonatorum.*

A rare variety of disease of the liver, which in some ways closely resembles Progressive Lenticular Degeneration, is known as Icterus Gravis Neonatorum. Pfannenstiel[6] was the first to separate this condition from the other more common forms of icterus of the new born. The disease is often

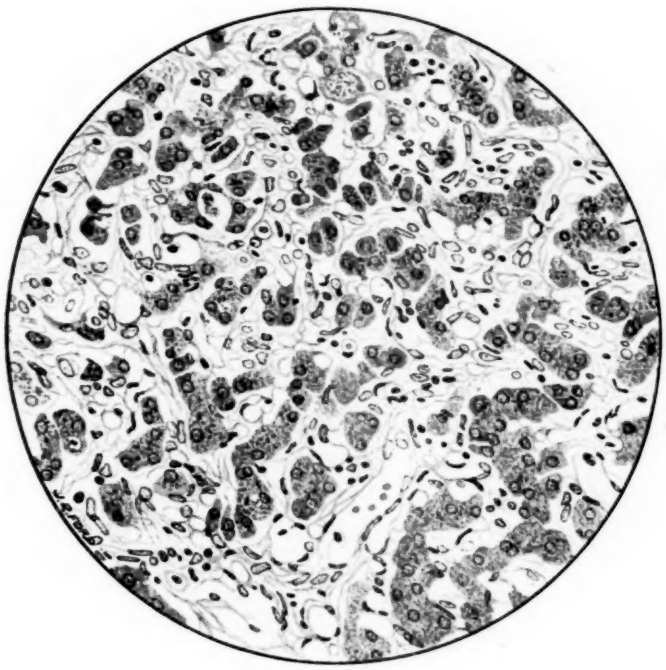

Fig. 4.—(X 225) Example of pericellular cirrhosis of syphilitic origin.

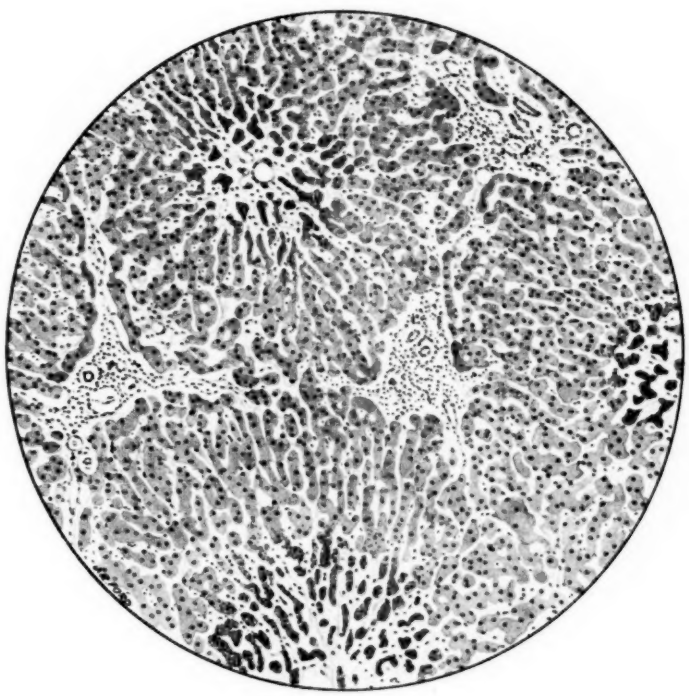

Fig. 9.—(X 60) Shows early cirrhosis of a monolobular type and pigmentation with bile granules of the cells towards the centre of the lobule. A higher magnification revealed the presence of numerous bile-casts lying like cement between the apposed hepatic cells.

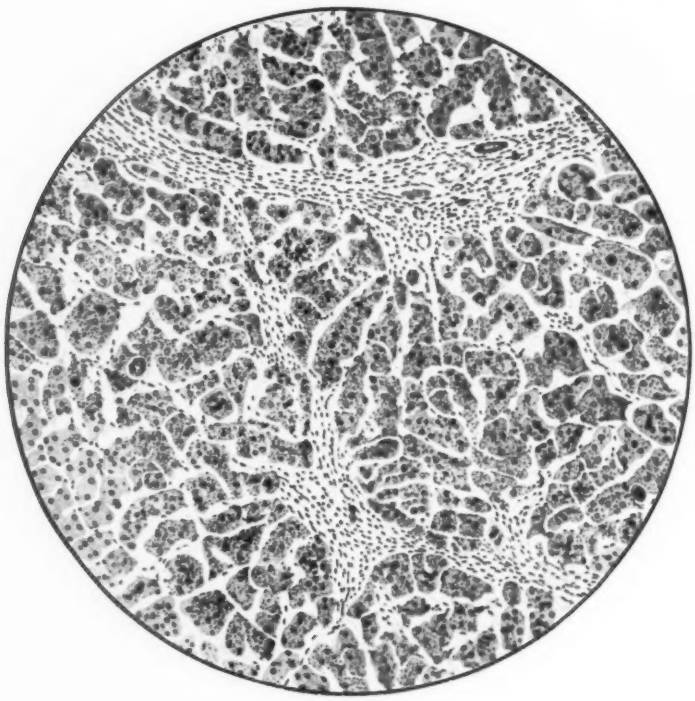

Fig. 10.—(X 135) From a case of Congenital Obliteration of the bile ducts. Bile pigmentation of the cells and bile-casts are conspicuous. The cirrhosis tends to be monolobular.

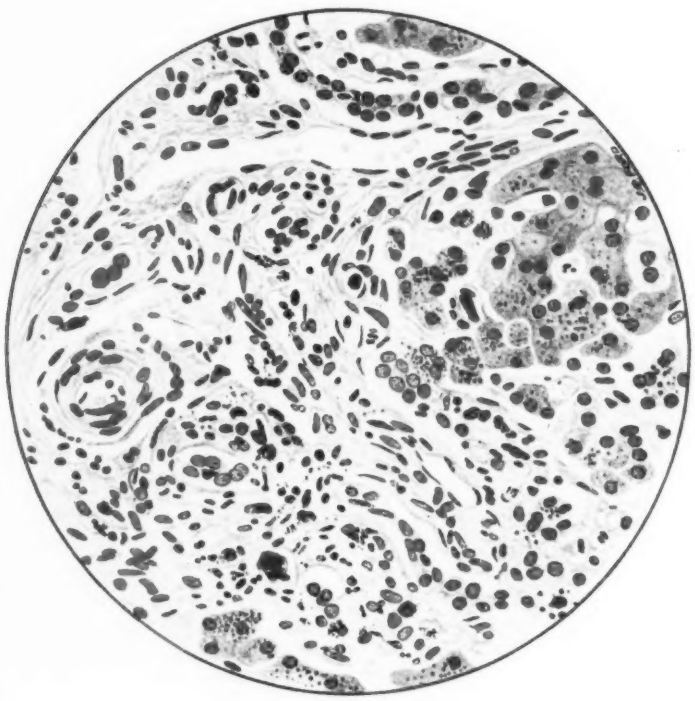

Fig. 11.—(X 300) From a case of Congenital Biliary Cirrhosis without Obliteration of the Bile ducts. The appearances are similar to those seen in Fig. 10.

familial, and a disposition towards hepatic disorders may be present in the family history. In Esch's[7] case the mother's father had suffered from severe jaundice, one of her sisters had been jaundiced, and another had suffered from gall stones. Beneke[8] recorded two cases in twins which died within the first three days of life.

In icterus gravis neonatorum the jaundice is usually intense, is commonly observed at birth, and death occurs in a few days, sometimes within twenty-four hours.

The nervous symptoms, in icterus gravis neonatorum, are not present at first, but develop later. They consist chiefly of head retraction, rigidity of the limbs, and tonic contractions of the upper extremities. These symptoms cannot be said to form a special syndrome of the disease, as they are sometimes seen in the terminal stages in patients dying from any form of hepatic cirrhosis.

The essential feature of the disease is the selective staining of certain parts of the central nervous system, the lenticular nucleus in particular, the corpus Luysii, nucleus dentatus, the olives and other gray matter at the base of the brain. These areas would appear to have a special affinity for the circulating pigment, and are stained a bright yellow, bile pigment being found in the bodies of the nerve cells. In no other type of hepatic disease, except that found in progressive lenticular degeneration, does the brain show any morbid changes.

Pathologically, there may seem to be very little evidence in favour of grouping such cases among the cirrhoses of the liver. In affected infants, dying in the first few days after birth, the liver is usually enlarged, of a normal colour and consistency, or it may be soft. The gall bladder contains viscid bile. Beneke, reporting on the pathology of Esch's case, which died on the day of birth, found no indication of increased connective tissue. The liver cells commonly contain bile pigments, and bile concretions are sometimes present in the intrahepatic ducts. In the more chronic cases, however, as for example in the fourth child in Pfannenstiel's family, which died on the twenty-first day, the liver was enlarged, coarse, and dark green; the spleen very rough and of a dark reddish-brown colour. Microscopically the interstitial tissue of the liver was irregularly broadened and had an œdematous appearance, with here and there small collections of cells. The liver cells contained bile and the cell-columns were very narrow; the bile ducts were widened at several points. These details are strongly suggestive of an early biliary cirrhosis, the fibrosis not commencing until after birth. We have met with no example of this type.

5. *Hepatic Cirrhosis in Splenic Anæmia (Banti).*

In splenic anæmia there may occur, in the later stages of the disease, a multilobular cirrhosis, thus constituting what is known as Banti's disease. This affection is stated to occur at any age outside infancy, the incidence being greatest between the age of twenty and forty. The spleen enlarges long before the liver, and may attain considerable dimensions. Other characteristics of the disease are anæmia, absence of leucocytosis, low hæmoglobin percentage, and the tendency to hæmorrhages, especially gastro-intestinal.

Although very few authentic cases have been recorded in children, cases do occur, which conform to this type more closely than to any other.

For example, in a case seen by one of us, a boy of four and a-half years, the spleen was noticed to be large at the age of two. In the same year he had a severe hæmatemesis. The child was extremely pale, had a cardiac murmur of the hæmic type, his spleen was

large, liver small. R.B.C. amounted to 2,750,000 per c.mm., W.B. C.2,400, and hæmoglobin 30%. He died suddenly after a profuse hæmatemesis. At autopsy large varices were found at the lower end of the œsophagus. The spleen was large and cicatrised, and there was considerable peri-splenitis. The liver was small, pale and firm. Histologically it showed early cirrhosis of the portal type.

Here we appear to have an example of a cirrhosis very different from the biliary type, in which the toxins presumably were carried to the liver by the splenic vein.

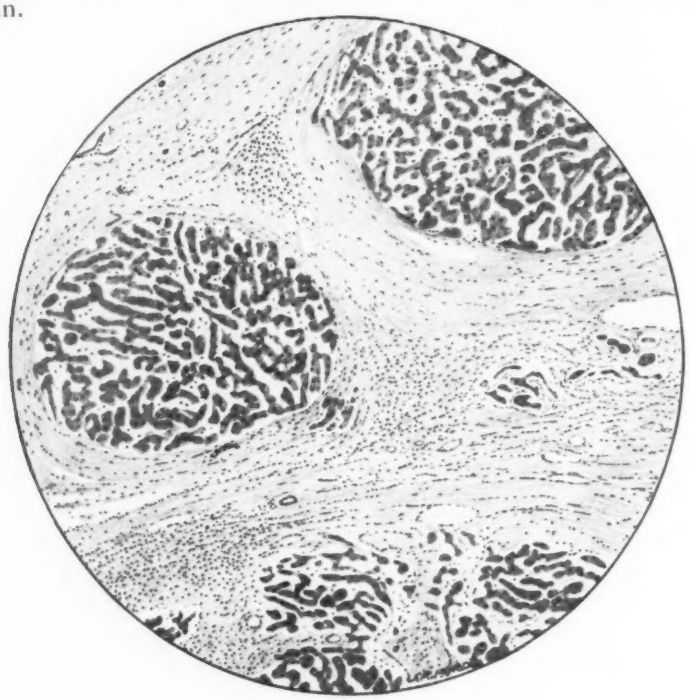

FIG. 6.

(x52) Section from a case of Banti's disease in a child showing remarkable degree of fibrosis. The cirrhosis was chiefly multilobular.

A second case observed by one of us illustrates in addition the interesting fact that whether the spleen or the liver appears to be the predominant organ, the clinical symptoms may in some cases be latent.

A boy, H. C., aged twelve years, had been attending school until the evening of his illness, and though of late his mother had thought him pale, and he had occasionally complained of abdominal pain, he was supposed to be in his usual health. This boy was brought to hospital late in the evening of December 30th, 1924, moribund, from repeated hæmatemeses, which had commenced on his return from school on December 29th, and had continued at intervals through the following day and night. On admission he was almost pulseless and died that night. His spleen extended to the umbilicus, and the edge of the liver could be felt, firm and well defined, below the costal arch. The liver was cirrhotic with numerous large " regeneration " nodules. The spleen was deep red. The remaining organs were avascular. The Wassermann reaction was negative. The necropsy showed an ulcer through an œsophageal varix.

6. *Cirrhosis associated with " Red Atrophy " or subacute Yellow Atrophy.*

Occasionally, in the course of a case of cirrhosis of the liver, an abrupt exacerbation of the symptoms, sometimes febrile, occurs, culminating in death; or without a previous history of hepatic disorder, a patient may

suddenly and unaccountably develop jaundice, pyrexia, enlargement of the liver, ascites, and die in a few weeks' time. In such cases sections of the liver microscopically show areas of necrosis of the parenchyma, other areas of degeneration of the hepatic cells, some extravasation of red corpuscles and varying degrees of fibrosis. The appearances correspond closely to what is known as subacute yellow atrophy in adults. Marchand states that anatomically there may be typical red atrophy of the liver, while clinically the course of the disease may be that of a chronic, possibly recurrent, type of the disease.

Recently R. Hutchison and D. Paterson[9] recorded the case of a child of fourteen months, who died after an illness lasting seven weeks.

The symptoms consisted of jaundice, enlargement of the liver and spleen, ascites, general œdema, and slight irregularity of the temperature. A blood count showed W.B.C. 80,000 per c.mm., which was suggestive of an infective cause. The Wassermann reaction was negative. Histologically there was a well marked cirrhosis of the liver of a mixed type, multi- and unilobular and intercellular. Extensive destruction of the cells was present besides areas of regeneration, and the newly-formed fibrous tissue was very cellular.

A similar case of our own is that of a girl of six years, who became jaundiced and died at the end of nine weeks.

There was nothing in her past history which would have led one to suspect disease of the liver. Following upon the jaundice other symptoms were enlargement of the liver, epistaxis, ascites, hæmaturia, putty-coloured stools, and vomiting. The blood count was not abnormal, and the Wassermann reaction was negative. The liver in this case was small, shrunken and "hobnail"; spleen considerably enlarged; pancreas fibrotic. A mixed cirrhosis, both multi- and monolobular was present, with extensive necrosis of liver cells and round-celled infiltration. Incidentally the thyroid gland was in an advanced stage of disintegration. There was no colloid, and no secreting cells were visible.

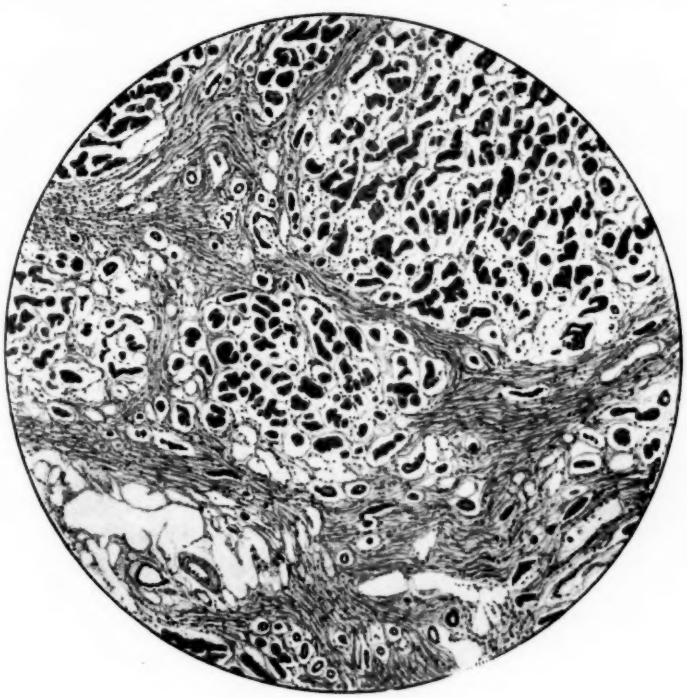

FIG. 7.

(x52) Represents the appearance seen on section of the liver in the case just described. The cell atrophy, however, unequal staining of the hepatic cells, and disappearance of many of the nuclei is not so obvious as in the original section.

Whether this rapid destruction of the liver cells marks some particular type of hepatic disease, or whether it is a possibility in all forms of cirrhosis is difficult to decide on account of the rarity of its occurrence. There is considerable evidence to show in many cases that there has existed a chronic but latent cirrhosis of the liver. This suggests sudden intensification of the poisons affecting the organ.

7. *The Biliary Cirrhoses* (A) *Hypertrophic Biliary,* (B) *Congenital Cirrhosis with or without Obliteration of the Bile Ducts, and* (C) *Obstructive Biliary Cirrhosis.*

In contrast to what is found in adults, cirrhosis of the liver in children is more often of the biliary or unilobular than of the portal type. These biliary cirrhoses, with the exception of the obstructive forms, are remarkable for the frequency with which they are familial.

(A) The form known as hypertrophic biliary cirrhosis, or Hanot's cirrhosis, occurs in the first half of life, probably commencing as a cholangitis and pericholangitis of the smaller bile ducts. Most of the cases described by Hanot were in adults, but later Gilbert and Fournier[10] published their observations on seven cases in children, the youngest of their series being a child of five years.

We have no record of a case of Hanot's form of cirrhosis, and it would appear to be a rare occurrence in this country if we may judge by the writings of others. It is possible that this type depends upon certain climatic or racial factors and that, in this country, we have cases akin, rather than identical. Hanot [11] defines this condition clinically as a chronic affection, characterised by permanent jaundice, febrile disturbances with exacerbations of the icterus, recurrent abdominal pain, considerable enlargement of the liver and spleen, and by an absence of ascites and dilatation of the superficial abdominal veins.

(B) The chief symptoms of the form of cirrhosis associated with obliteration of the extrahepatic bile ducts (congenital biliary cirrhosis) are jaundice, usually intense, present at birth or appearing shortly afterwards, and considerable enlargement of the liver, and to some extent of the spleen. Œdema of the extremities and ascites are sometimes present. Pallor of the stools is always observed, although a small quantity of normal coloured meconium may be passed at first. Death may occur after a period of a few days or weeks, usually before the fourth month, and always, according to Dr. John Thomson, under the year. Cases of congenital biliary cirrhosis without obliteration of the bile ducts, or in which there is only a partial interference with the passage of bile into the duodenum, are clinically indistinguishable from those which present obliteration of the ducts. Jaundice may be present at birth, or appears a few days or weeks afterwards, and the stools become pale. With few exceptions death occurs within the year, and usually before the sixth month.

Two examples are of interest in so far as the onset of jaundice was later in the case with obliteration of the bile ducts than in the one in which the ducts were patent. In the former jaundice was first noticed at the age of seven weeks, and the liver was found to be considerably enlarged. Jaundice in the second case appeared at the end of the third week. The stools became pale, the urine green, and the liver was slightly enlarged. Death occurred in the tenth and eighth weeks respectively. The Wassermann reaction of the blood in both cases was negative.

(C) Obstructive biliary cirrhosis in children is a rare event. The common causes in adults, such as cancer of the head of the pancreas and impacted stone in one of the large bile ducts, are not met with below the age

of puberty. It has, however, been stated to occur as the result of pressure on the common bile duct by tuberculous glands in the hilum of the liver. Considering the large number of cases of general tuberculosis in which large caseating glands are found between the head of the pancreas and hilum of the liver, and in which no evidence of biliary obstruction is present, either during life or at autopsy, this method of production appears to us doubtful.

Two cases of obstructive biliary cirrhosis were observed recently at Great Ormond Street, one of which, Dr. Still's case, was recorded in the *Lancet*,[12] May 9th, 1925, and the other in the same journal,[13] June 27th of this year. Dr. Still's case was that of a girl of six years, in whom an intermittent over-distension of a congenital cystic abnormality of the common bile duct had brought about a secondary cirrhosis of the liver.

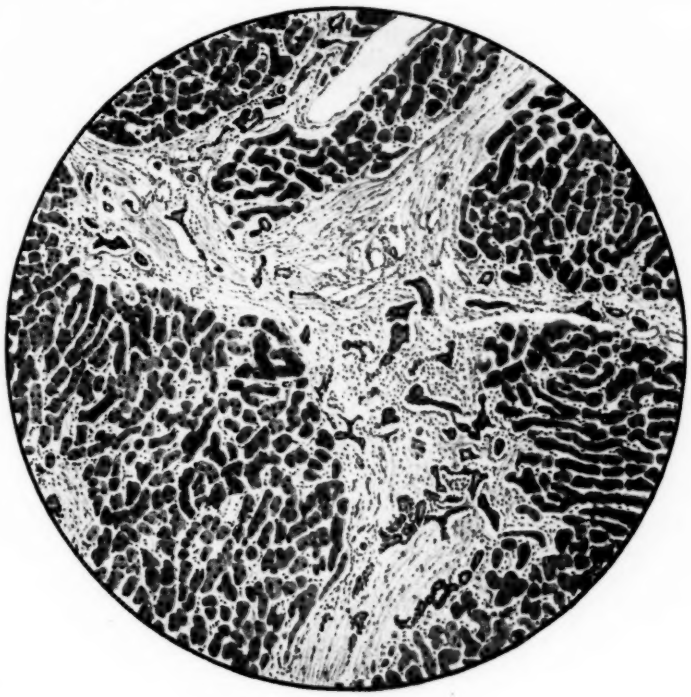

FIG. 8.

(x67) Section of the liver from Dr. Still's case showing cirrhosis and an apparent increase of bile ducts. The cirrhosis was of a mixed type.

The liver was found to be slightly enlarged, firm and finely granular superficially. Microscopy showed some thickening of the portal tracts, and the fibrosis was specially distinct around the smaller bile ducts, spreading also into the lobules and compressing the peripheral ends of the columns of liver cells, thus giving the appearance of pseudo-bile ducts. The bile ducts themselves were not dilated. In the other case secondary sarcoma of the pancreas was the cause of obstruction in a girl of ten years. The liver, which was considerably enlarged and of a dark green colour, showed no evidence of metastatic invasion. An early definitely unilobular cirrhosis was present, with thickening of the portal tracts, bile casts in the small bile ducts, and granules of bile pigment in the liver cells.

COMPARISON OF THE TYPES OF BILIARY CIRRHOSIS.

When we consider biliary cirrhosis we are at once met by the numerous writings devoted to the proof that there is a distinct pathology for the various

types. Yet we are left doubtful as to whether there is evidence of sufficient weight to allow us to go further than to consider the distinctions to be rather those of degree than of nature.

(A) Hanot[14] certainly considered that the so-called hypertrophic biliary cirrhosis possessed peculiarities sufficient to isolate it from all other forms. His definition was that of an interstitial hepatitis, both extra and intra-lobular, with catarrhal changes and a great increase in the number of the small intrahepatic bile ducts. The liver was described as being usually of a dark green colour, enlarged, and having a smooth, or finely granular surface, the fibrosis being chiefly unilobular in type. In the portal spaces the connective tissue was less dense than in multilobular cirrhosis, and signs of fibrosis and cellular reaction were more evident in relation to the sheaths of the biliary than of the vascular channels. Catarrhal changes, with desquamation and renewal of the epithelial cells lining the inter-lobular bile ducts were observed, and many of the smaller ducts were found to be in a state of obliterative cholangitis.

Constriction of the hepatic vessels and of the branches of the portal vein was absent. In fact some dilatation of the latter was frequently present in the portal spaces. The hepatic cells were for the most part little altered, except where the intra-lobular cirrhosis was well marked, and then the columns of the liver cells were often seen to be flattened and squeezed together, or separate cells at the periphery of the lobule were surrounded by connective tissue as in a pericellular cirrhosis. Pigmentation of many of the hepatic and endothelial cells lining the smaller bile ducts was noticed, and also the presence of bile casts between the columns of compressed liver cells and in the smaller extra-lobular bile ducts. Attention was particularly drawn to the absence of contraction of the fibrous tissue, which might be accounted for by the unobstructed state of the blood supply. Hanot stated that the liver, in a small number of his cases, did actually lose some of its increased bulk in the later stages of the disease. The cirrhosis in these latter cases was found to be of a mixed type, both unilobular and multilobular, but chiefly the former. In explanation it was suggested that a portal or atrophic cirrhosis had arisen as a late complication, the result of a general toxæmia, consequent upon the absorption of poisons from the infected biliary reservoir.

The apparent increase of bile canaliculi at the periphery of the lobules in Hanot's hypertrophic biliary cirrhosis is a feature which has aroused much interest. The question is whether many of them are really permeable, and for this reason they are usually referred to as pseudo-bile ducts. Undoubtedly some appear to be developed in a genuine effort to maintain a connection between the larger ducts of the portal spaces and the peripheral ends of the column of liver cells. Others are probably only columns of newly-formed endothelial cells of the biliary type, which it is supposed play a small part in the formation of hepatic cells in the regeneration of the lobule (MacCallum). Or again, the appearance of bile ducts may be simulated, as has been pointed out by Ford,[15] by the compression and squeezing together of columns of liver cells at the periphery of those lobules which show much intra-lobular fibrosis.

Lefas[16] examined the pancreas in several cases of hypertrophic biliary cirrhosis and found a slight amount of interacinar fibrosis. Moreover, in the vicinity of the islets of Langerhans he stated it was not unusual to observe small fibrous foci, many of which enclosed a number of cells having an exactly similar appearance to that of the pseudo-bile ducts in the liver.

The explanation of the cirrhosis has given rise to much speculation. Gilbert and Fournier[11] considered that organisms normally present in the

bowel invaded the bile ducts and were the cause of cholangitis. Boinet,[17] who suggested chronic intestinal disturbances as the cause, recorded a family in which the father and four children were all affected at one time or another by a febrile disturbance resembling typhoid fever. The fever was followed by jaundice and enlargement of the liver and spleen in the father and two elder children. The two younger children and another, in whose case fever was not mentioned, had big spleens, but their livers were not enlarged. Boix,[18] who held that the enlargement of the spleen preceded that of the liver in hypertrophic biliary cirrhosis, stated that the children of a parent with this disease were sometimes found to have large spleens without any other signs. He considered there was a hepato-splenic infection of a specific type.

Against the theory of an ascending infection from the bowel, there is the absence of any evidence at autopsy of inflammation of the duodenal mucosa. Also, with the prevalence of disorders of the alimentary tract in childhood, this form of cirrhosis would be expected to be a much more common occurrence. It is more likely to be, as Sir H. Rolleston suggests,[19] a local result of a chronic general toxæmia, with the conveyance of the toxin to the smaller bile ducts by means of the hepatic artery.

When compared with the histological features of the other forms of biliary cirrhosis there is very little that is peculiar to Hanot's form. In his type the course of the disease is certainly more chronic, and for this reason the microscopical appearances are the more outstanding, but the liver is usually dark, bile-stained and often green, in the congenital and obstructive forms of biliary cirrhosis. Pseudo-bile canaliculi are common to all forms of hepatic cirrhosis, though less often seen in the syphilitic variety. Bile casts in the smaller ducts and masses of bile in their lining cells and in the hepatic cells are constantly found in cases of congenital obliteration of the bile ducts. Some fibrosis of the pancreas occurs also in all long standing cases of hepatic cirrhosis. The spleen tends to be enlarged to a less extent in the portal than in the biliary type with the exception of the obstructive form, which is usually of short duration.

A type of cirrhosis with very little jaundice, which resembles hypertrophic biliary cirrhosis in the majority of its histological features, must also be mentioned. Examples of this kind were described by Hayem[20] in 1874, and referred to later by Hanot as cases of " sclerose sans ictere." Here the liver is greatly enlarged, smooth, not dark green but usually of a mottled yellow colour, and microscopy shows little or no alteration of the bile canaliculi. In all probability this is the same type of hypertrophic portal cirrhosis described by Cheadle, to which reference has already been made. Hayem's examples of this condition were in adults.

(B) In congenital obliteration of the bile ducts the cirrhosis is often of a mixed character, but speaking generally is chiefly monolobular. Externally the liver may be smooth or finely granular, but both extra- and intra-lobular cirrhosis may occur. Degenerative changes of the hepatic cells on the other hand are more common than in the hypertrophic biliary form, and many of the cells in the more affected lobules are swollen, vacuolated, and their nuclei invisible. The bile ducts are not dilated.

Here once more opinions differ as to whether the cirrhosis is primary or secondary to the occlusion of the larger bile ducts. Dr. John Thomson[21] on the one hand, considered that a malformation of the ducts was the essential lesion, and that subsequent catarrhal changes, occurring usually in intra-uterine life, led to the occlusion and obliteration of the ducts. At the same time biliary cirrhosis was produced, as a result of obstruction of the bile and the spread of the catarrhal changes to the small intra-hepatic ducts. The

theory of a primary congenital abnormality is strengthened by the frequency with which cases of the kind occur in more than one child of the same family. Holmes,[22] after reviewing all the recorded cases of congenital obliteration of the bile ducts up to 1916, came to the same conclusion.

In regard to the possibility of inflammatory changes occurring in fœtal life, it is well known that peritonitis can occur. Adhesions between the liver and peritoneum have been described in this and other morbid conditions of the newly-born. A localised peritonitis in the region of the common and hepatic ducts has been suggested as a possible cause of their occlusion. Thomson, however, considered that the peritonitis, when present, was secondary to the malformation of the ducts.

Sir H. Rolleston,[23] on the other hand, regarded the cirrhosis as the initial lesion, and the fibrosis and obliteration of the larger ducts as secondary to a descending cholangitis. A primary cirrhosis would certainly help to explain those cases, which, though clinically indistinguishable from those with obliteration of the ducts, anatomically show no occlusion of the latter. Moreover, examples of this type in which no obliteration of the ducts exists, are by no means uncommon. In the case recorded by Keith Gordon,[24] jaundice was present at birth. At autopsy, however, the bile ducts were found to be patent. In Dunn's[25] case also the ducts were not occluded. The infant did not begin to be jaundiced until the twelfth day after birth.

Those in favour of the view of a primary cirrhosis suggest that toxic substances, from the maternal blood, enter the fœtal circulation by the umbilical vein. The irritant bodies would then pass partly to the liver directly, and partly into the general circulation, whence they would also

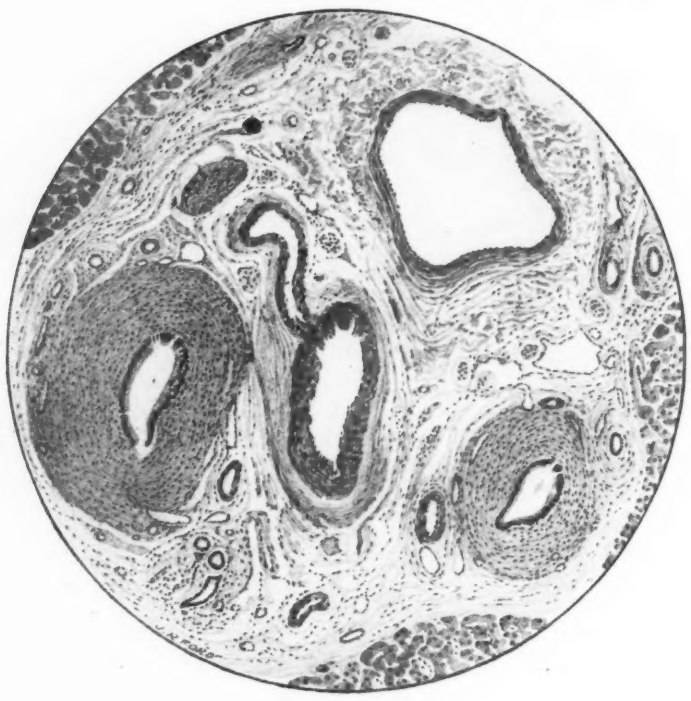

FIG. 12.

(x45) Is from the same case as Fig. 11. The section is of one of the larger portal tracts and shows an extraordinary degree of thickening of the bile ducts.

reach the liver by the hepatic artery. West[26] considered this method of distribution would account for the frequency with which the fibrosis, in this form of cirrhosis, is both unilobular and multilobular.

(c) In regard to the obstructive type complete and sudden obstruction of the common bile duct is known to give rise to dilatation of the bile ducts and widespread degeneration of the liver cells. The occurrence of cirrhosis, according to Rolleston,[27] is in such cases the result of an added inflammatory process. When obstruction and inflammation are present, there result an extra- and intra-lobular cirrhosis. The bile ducts remain dilated but show signs of catarrhal inflammation and fibrosis spreading to the surrounding tissues. The inflammation spreads from the larger to the smaller ducts. In time a mixed form of cirrhosis is produced both unilobular and multilobular. The latter is possibly due to the absorption of poisons into the portal system from the alimentary tract, in which putrefactive changes are in excess owing to the absence of bile. Degenerative changes of the hepatic cells are often more evident in this type than in the other forms of biliary cirrhosis.

There would appear then to be many common features in the hypertrophic biliary, the congenital infantile, and the chronic obstructive forms of biliary cirrhosis. The macroscopic changes are fairly similar, and their microscopy essentially alike, for in all the fibrosis is related primarily to the bile ducts and becomes both extra and intra-lobular in distribution. Jaundice, once it has appeared, is usually a permanent symptom of each type, and the degree of biliary stasis, as indicated by bile casts in the ducts and between the columns of liver cells and bile granules in the cells themselves, is proportionately far greater than is found in the case of a portal cirrhosis. In the biliary cirrhoses infection or toxic irritation of the biliary reservoir appears to be essential to their production, and whether this inflammation is primary, or consecutive to a congenital or mechanical obstruction is of secondary importance. In obstructive biliary cirrhosis the dilatation of the intra-hepatic ducts is best explained by the onset of the obstruction preceding the inflammatory reaction.

The interesting speculation arises whether the congenital form, if slight in degree, may not later develop into a hypertrophic biliary cirrhosis, and there are suggestive cases bearing upon this theory.

In a case recorded by Smith,[28] an infant recovered from an attack of icterus neonatorum after fourteen days and subsequently developed hypertrophic biliary cirrhosis of the liver with a large spleen, dying at the age of fourteen and a-half years. The initial jaundice was slight, but recurred with added severity during the terminal illness. Whipham[29] described the case of a girl who was born with icterus, which lasted six weeks. Jaundice reappeared at the sixth year, and the liver and spleen were discovered to be much enlarged.

Special Features.

Finally, we come to certain remarkable features associated with cirrhosis of the liver in the young. The first is the familial tendency, the second infantilism, and the third, a feature also of adult life, the liability to hæmorrhage.

The familial tendency has attracted the attention of many writers, and there are numerous examples in the literature (Hasenclever,[30] Parkes Weber,[31] Dreschfeld,[32] Finlayson[33]). For example, Byrom Bramwell[33a] described the case of a boy, nine years of age, who died of cirrhosis of the "hobnail" type, three of whose sisters had apparently died of the same disease. Schuscik[34] recorded the case of a girl, aged two years, with

hypertrophic biliary cirrhosis. Of the other children in the family two boys were apparently healthy, but two girls had died jaundiced at the ages of two and a-half and two and a-quarter years respectively. The parents were healthy, but the paternal grandfather had been jaundiced for many years.

The majority of these cases with a familial history belong to the group of biliary cirrhoses, and to such Parkes Weber has given the name "family biliary cirrhosis."

The question naturally arises as to the explanation of this familial tendency. Is there some toxic cause peculiar to the mother which develops in pregnancy and affects the fœtus through the placenta, or is there a repetition of a developmental malformation? Considering the scant knowledge at our disposal on the subject of disease *in utero* it is impossible to make any dogmatic statement, but we are inclined to support the view of a primary developmental defect in these cases. That obvious congenital defects of development may occur in the liver as well as in any other organ is well exemplified by the following three cases. Two are cases of cystic liver, associated with cystic disease of the kidneys; one an unrecorded case of Sir Archibald Garrod's, the other published by Dr. Still.[35] Both are from the case reports of the Great Ormond Street Hospital, a boy, aged nine months, and a girl, aged eight weeks. The kidneys, in either case, were greatly enlarged and of the "honeycomb" variety. The livers were of a normal size, hard and slightly roughened externally. Microscopical examination showed a great increase of fibrous tissue about the portal canals and a large number of irregular branching cavities, situated mostly in the fibrous tissue. These cavities were lined by flattened columnar epithelium. In all probability

FIG. 13.

(x45) Is from a specimen in the Museum at Great Ormond Street Hospital, the liver of the case described by Forbes. An extensive degree of cirrhosis is apparent.

they were remains of the spaces between the cell cylinders or groups of cells of entodermal origin, which are derived from the duodenal diverticulum to form the liver. If development proceeds normally, these spaces become narrowed and surrounded by fever cells, and are supposed to become finally bile ducts.

The third case, recorded by Forbes,[36] was a girl of two years and eight months. She presented cirrhosis of the liver, "honeycomb" lung, and tuberculosis of the tonsils, mediastinal and mesenteric glands. No trace of tubercle was discovered in the liver, lungs or pancreas. The liver was greatly enlarged, slightly roughened, pale and hard, and in section showed scattered islets of fibrous tissue, which were mainly white, but at some points bile stained. There was no evidence, other than the glands, to point to tuberculosis as the cause. Although not being familial, attention is particularly drawn to these three cases as showing the occurrence of errors of development of the liver, in addition to obvious abnormalities in other organs.

Infantilism.

Infantilism as a result of chronic disease of a vital organ is well recognised, and illustrated in the young by the occurrence of this feature in "cœliac disease" in addition to the hepatic form.

Arrest of growth is particularly striking in these hepatic cases, possibly because the large abdomen emphasises the short stature.

Arthritic changes of the fingers and clubbing of the finger tips have also been noticed in chronic hepatic cirrhosis.

Hæmorrhage.

Hæmorrhage occurs in two ways; there may be varices of the lower end of the œsophagus or rectum, and fatal bleeding as exemplified in two of our cases of the Banti type; or there may be general bleeding from the gums and under the skin and elsewhere associated with a widespread toxic condition.

The first type is the result of a portal cirrhosis and local venous high tension. The second probably the result of some toxic agent affecting the blood or capillary walls.

The toxic agent may be actually produced by the disordered hepatic metabolism; or result from inability of the damaged organ to maintain the supply of protective substances normally produced by healthy liver tissue. Bouchard[37] is of the opinion that bleeding of this type is arterial and not venous, as in a case recorded by him of alcoholic cirrhosis, accidental scratching of a nævus on the face and of one on a finger had caused jet-like bleeding in both instances.

Conclusion.

Lastly, as to the nature of the four cases recorded in this paper, the first, that of a girl of nine with intermittent jaundice, epistaxis and hæmatemesis, is most likely to be a case of portal cirrhosis, associated with tuberculosis, possibly mesenteric, and without congenital predisposition.

In the cases of the brother and sister, who had enlargement of the abdomen from birth and very little jaundice, we are probably dealing with a form of hypertrophic cirrhosis, similar to the *sclerose sans ictere* described by Hayem. Here we think the cirrhosis is of portal rather than of

biliary origin, both because of the transitory nature of the jaundice, and because a hypertrophic form of portal cirrhosis is known to exist, as pointed out by Cheadle. Presuming our supposition to be correct these two cases are specially interesting owing to the rarity of a familial occurrence of the portal type, as compared with the biliary form of hepatic cirrhosis.

The history of the fourth case is too short to justify any dogmatic statement, but the fact that the children in a family almost simultaneously developed jaundice suggests an infective cause and a catarrhal jaundice. In the child the liver undoubtedly enlarges more than in the adult in catarrhal jaundice, and this enlargement may remain for weeks. In this case, however, the size and hardness of the liver, and the duration of the jaundice were unusual. Also the outbreak of fever with the rapid and great enlargement of the spleen as a late event were features we have never observed in the catarrhal jaundice of childhood. On the other hand the remarkable subsidence of the liver and spleen before the child left hospital favoured some degree of biliary obstruction rather than cirrhotic changes in the liver.

In conclusion, then, it is obvious that many difficulties beset the clinical interpretation of cases of hepatic cirrhosis in children. It is often impossible to be certain either of the nature of the cirrhosis or of its origin. The latency of the condition before symptoms manifest themselves is a striking feature of many cases. The pathogenesis of the congenital and familial forms of cirrhosis rests obscure.

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ADRENALIN

IN

Severe Rheumatic Heart Block.

BY

G. A. SUTHERLAND, M.D., F.R.C.P.

There are two subjects to which attention will be specially directed in this paper. The first is the value of adrenalin in conditions of heart block when the symptoms are so severe that death seems imminent. The second point is the early appearance of a definite and grave cardiac lesion as the result of rheumatic infection, and before any other evidence could be detected as to what the nature of the illness was.

My attention was directed to the use of adrenalin in the Stokes-Adams syndrome by papers by Phear and Parkinson[1] and Parkinson and Bain.[2] They found that it was possible for heart block to be reduced, and even for complete heart block to be abolished, by the subcutaneous injection of adrenalin. A very important point which they seemed to establish was this, that the ventricular standstill which is often accompanied by such alarming symptoms may be abolished or much modified by this treatment. The suggestion seemed so valuable that I made a mental note of it for use when an emergency presented itself.

The second point is the involvement of the heart muscle at a very early stage of rheumatic infection. There is a valuable paper by Parkinson, Hope Gosse, and Gunson[3] recording a study of fifty cases of acute rheumatism as regards the heart and its rhythm. In 15 of the 50 cases (30 per cent.) some degree of auriculo-ventricular heart block developed, but it was usually merely a lengthening of the A-C interval and led to no symptoms. Had they not been making frequent polygraph tracings the heart block would usually have been overlooked under ordinary clinical examination. They found no case of complete heart block. What they have established is that the part of the myocardium known as the conducting tissues is not infrequently slightly affected by rheumatic infection in the acute stage. Definite signs of myocardial involvement, such as dilatation, are always difficult to determine and are not usually present in the early stages of rheumatic infection. It came, therefore, as a great surprise to me to find, as in the following case, that the conducting tissues might be selected by the rheumatic poison before there was any evidence of rheumatism, and that alarming symptoms of heart failure might supervene before one had any clear idea as to the nature of the illness.

My experience of heart block at an early stage of rheumatic infection does not stand alone. In 1916 Dr. Paul White[4] wrote as follows :—" The detection of an acute heart block prior to the finding of other signs of rheumatic fever infection is so unique and important as to deserve special mention." His patient was a lad of 18 years who after four days of indefinite illness was found to have partial heart block with many dropped beats. After admission to hospital his joints became swollen and he passed through an ordinary attack of acute rheumatism. In this patient the heart block was accidentally discovered and had not been the cause of any special symptoms. The author emphasises the facts that the myocardium not only gave the first evidence of the importance of the illness but also showed at

least temporary damage, while no evidence was found of endocardial or pericardial involvement. Another example of the involvement of the conducting tissues by the rheumatic poison before other evidences of the disease had shown themselves has been recorded by Dr. Daniel Routier.[5] His patient had complete heart block, with attacks of unconsciousness, after a fortnight's illness characterised by gastro-intestinal symptoms. Articular lesions developed later and the subsequent course was that of an attack of rheumatic fever. He emphasises the selective action of the rheumatic poison on the conducting tissues of the heart at an early stage of the disease. A case of partial heart block occurring during an attack of rheumatism has been recorded by Cowan, McLeod, and Paterson.[6] The patient was a girl of 17 years who was admitted to hospital suffering from acute arthritis. The pulse was found to be irregular and tracings showed that this was due to defective conduction in the A-V bundle, every second or third auricular stimulus failing to reach the ventricle. There was no evidence of any other cardiac lesion save that in the conducting tissues. The irregularity of the heart gradually became less marked and eventually the A-V action became normal. Another case of complete heart block in a youth, accompanied by attacks of syncope, is recorded by Laursen.[7] He was suffering from acute articular rheumatism, and under treatment by salicylate of soda made a good recovery as regards the rheumatism and the heart block. The author considers that it was clearly a case of rheumatic infection of the bundle of His, without other cardiac involvement. Other cases of heart block during rheumatic fever have been recorded by Magnus-Alsleben[8] and by Lundsgaard,[9] so that the liability of the conducting tissues of the heart to be attacked by the rheumatic poison has been fully demonstrated.

The history of my patient's illness is as follows:—A schoolboy of 17 years was noticed by a brother at 3 a.m. to have a fit. The patient had just returned to bed after having risen to take a drink of water. From 3 a.m. to 5 a.m. he had a series of fainting turns, and at 5 a.m. another fit. A doctor was summoned and found the condition to be as follows:—Numerous fainting turns occurred in which the patient turned pale, but did not lose consciousness. He complained of the faint feeling. In the more severe attacks or " fits " he became pale, the legs and arms were fixed and he lost consciousness; some twitching of the limbs and face occurred, he breathed deeply, the face became flushed, and he recovered consciousness. The severe attacks occurred only occasionally until mid-day and then became more frequent. After a severe attack there was usually vomiting or violent retching. Everything swallowed was promptly vomited. He was seen by me at 2 p.m. on the same day. The boy was feeling tired and exhausted. The pulse was at times steady and regular at 80 per minute, and at other times irregular with pauses of varying length. These pauses were characterised by a feeling of faintness on the part of the patient. During 20 minutes the pulse stopped twice for long intervals and each time a " fit " as described above occurred—clearly an example of the Stokes-Adams syndrome. The periods of ventricular standstill were so prolonged that one wondered if the ventricle would ever resume beating. He seemed too dangerously ill to allow of a polygraph tracing being taken. Examination of the heart showed a strong impulse at the apex, normal heart sounds, and a pulmonary systolic murmur.

As regards the cause of this attack there was not much information to be obtained. Two days previously the boy had been at Lord's cricket ground for practice at the nets, and had arrived home very tired, with a temperature of 99·5° F. The next day he felt better, but remained indoors as he still

felt rather slack. Apart from this he complained of no symptoms of discomfort. As regards his previous health he had always been delicate. Some three years ago he had had an attack of tuberculous pleurisy with effusion. He had never suffered from rheumatic infection and his doctor had never detected any sign of heart disease. Three weeks previously he had been in the sick room at school for a few days with sore throat and vomiting. Influenza was prevalent in the school at the time and he was regarded as a victim. He had recovered completely from this attack.

The diagnosis of severe heart block was easily made but its successful treatment was a difficult problem. There was no indication as to the cause of the condition. It was decided to try the effect of adrenalin. Four minims of adrenalin solution (1-1,000) were given hypodermically. After this I waited for 20 minutes, during which time the boy had very few faint turns and no severe ones. He was seen again three hours later. There had been no further severe attacks, no faints, and no vomiting or retching. He had slept quietly for an hour and a half and had then taken some nourishment. As a matter of fact from the time of the first injection of adrenalin there occurred no more attacks of the Stokes-Adams syndrome, and very few faint turns. The accompanying polygraph tracing shows the state of heart block present at this second visit. He was given a similar injection of adrenalin the same evening; two similar injections on each of the two following days; and one injection daily for the next two days. The total amount was 32 minims of adrenalin solution in five days.

The progress of the case threw a flood of light on the nature of the severe onset. The night of the onset his temperature was 100° F. and on the following morning 101° F. He sweated profusely during the night and complained of pain in the left ankle, which was found to be swollen and tender. He passed through an ordinary attack of rheumatic fever, the temperature reaching its maximum (102° F.) on the second day, and falling to normal on the fifth day under salicylate of soda treatment. Other joints were swollen and tender, including the right wrist, the right ankle, and the left elbow. He progressed well and in a week was convalescent. When seen three months later the boy was in his usual state of health, the heart was free from any abnormality, and there were no symptoms of any cardiac disability. Six months later he was taking his full share in all the school sports.

The course of this attack of heart block can be best studied in connection with the polygraph tracings. The tracing (Fig. 1) was taken 11 hours

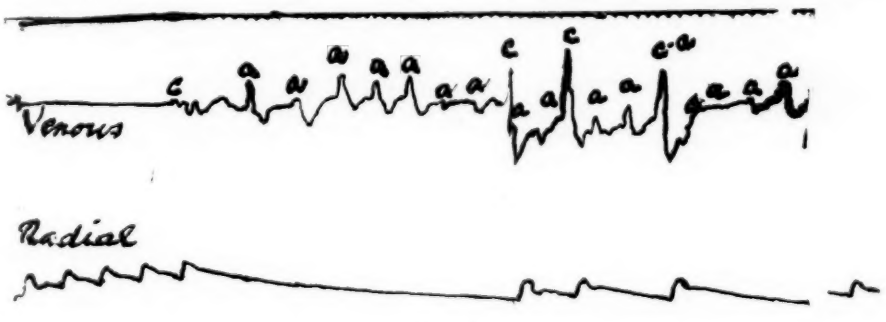

FIG. 1.

after the first " fit " was noticed and three hours after an injection of adrenalin. It will be seen that the ventricular rate is at times very irregular, varying from 35-40-45 per minute, while the auricular rate is regular at 90

per minute. The longest ventricular standstill in this tracing is one of six seconds, but there was no accompanying complaint of faintness by the patient. During the following night there were several faint and giddy turns, which were relieved by an injection of adrenalin. These were probably the result of a more prolonged ventricular standstill. From that time onwards there were no symptoms of any kind associated with the heart block. On the third day of the illness another tracing (Fig. 2) was taken.

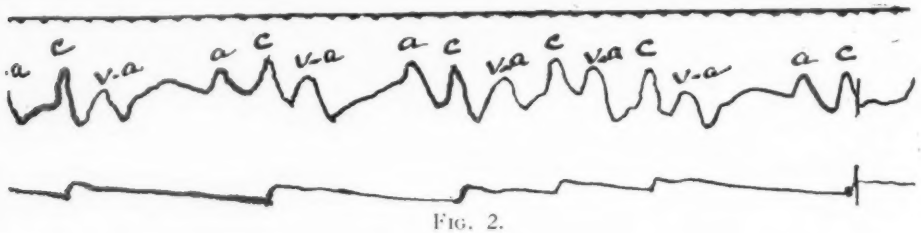

FIG. 2.

This shows an auricular rate of 70 with a ventricular rate of 45-50. There is a long A-C interval, namely, two-fifths of a second, and at times the ventricle fails to respond to the auricular stimulus. There are no long ventricular pauses as before. Three days later another tracing (Fig. 3) shows

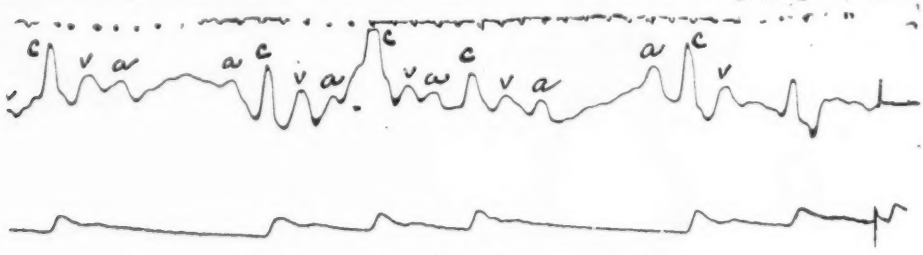

FIG. 3.

much the same condition, with the auricle beating more slowly at 60 per minute. Four days later the tracing (Fig. 4) may be taken as normal.

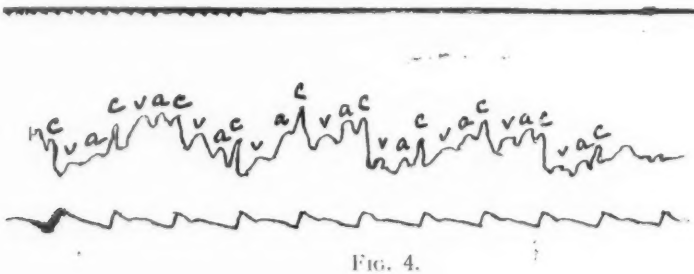

FIG. 4.

Auricle and ventricle are beating regularly at 58-60 per minute. There are no missed beats, and the A-C interval is only very slightly increased. Later tracings showed the rhythm to be normal in every way.

In this case the conducting tissues of the heart were involved at an early stage of the rheumatic infection, with possibly other myocardial involvement, but in areas which are silent as regards symptoms. One cannot conceive of a severe inflammatory process as the condition present or that the production of Aschoff's nodes was going on. The cessation of symptoms and the rapid recovery are against such a view. It seems to be more probable that there was some toxic disturbance in the conducting tissues, possibly some œdema or vascular disorder, and that the local disturbance

was a temporary one. The joint symptoms in rheumatic fever are often temporary and fleeting and I think it was Sir Archibald Garrod who suggested that the arthritic phenomena might be toxic in origin as contrasted with the endocardial and pericardial phenomena which are inflammatory in character. Such a view would appear to be the best explanation of a temporary disturbance in the conducting tissues of the heart.

Soon after the onset of auriculo-ventricular dissociation in this lad attacks of the Stokes-Adams syndrome developed and threatened life itself by a prolonged standstill of the ventricles. How near he was to a fatal issue it is impossible to say, but from the observer's standpoint it may be stated that the symptoms were very alarming. The question arises as to whether adrenalin really checked the attacks or whether they would have ceased naturally and without it. There is very strong evidence against the latter view. At the time adrenalin was given the attacks had been going on for 11 hours, and were becoming more frequent—two in the last 20 minutes. Adrenalin was given because of the published reports as to its value in cases of severe heart block. It was not a case of the haphazard trial of a drug but an attempt to repeat the experience of other observers. No other drug in my experience has ever produced a result comparable to that which followed the adrenalin injection. From the time of the injection no further attacks of severe heart block (Stokes-Adams syndrome) occurred. From that time no sign of cardiac embarrassment or danger appeared. The boy passed from a condition of imminent danger to one of ordinary illness.

What is the exact action of adrenalin in such cases? Clinically speaking one can say that it had checked the prolonged standstill of the ventricles which was the immediate danger. It had not removed the auriculo-ventricular dissociation which persisted for some days longer although always to a diminishing extent. Pharmacologically speaking one has a difficulty in determining the exact action of adrenalin, a difficulty comparable to that still existing as regards digitalis. The problem is as to whether these substances act on the heart muscle directly or through the nerves supplying the heart. It is taught that adrenalin stimulates the sympathetic nerves, thereby increasing the activity of the conducting tissues, and also that it acts directly on the ventricular muscle, thereby increasing the rate of the ventricles. Under normal conditions one cannot see how this latter action could apply, because the ventricular rate is always dependent on the auricular rate and follows it closely. When there is auriculo-ventricular dissociation with a very slow ventricular rate anything which increased the rate of the ventricles would be helpful. This is what adrenalin appears to do, either by direct stimulation of the sympathetic or by direct stimulation of the ventricle. The result is that a tendency to prolonged standstill of the ventricles, from which come the dangerous symptoms, is checked or abolished as long as the effect of the adrenalin lasts. It may be that the idio-ventricular mechanism which exists in every heart, and which comes into play in cases of complete A-V dissociation, after a longer or shorter time, may be stimulated into activity by adrenalin in those cases of prolonged ventricular standstill.

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REMARKS ON THE DEFORMITY OF PES CAVUS.

BY

A. S. BLUNDELL BANKART, F.R.C.S.

Pes cavus is a condition in which the arch of the foot is abnormally increased. But, at the outset it is difficult to say what is a normal arch, or rather when exactly a high arch ceases to be normal, because many apparently normal people have high arches, and others have low ones. It is not enough to say that an arch is abnormally high when it is sufficient to give rise to symptoms, because many deformed feet are painless and functionally useful.

The arch of the foot is essentially a dynamic condition, it is an expression of the muscular activity of the foot, and it varies both in different individuals and in the same individual at different times. When the muscles are strongly in action, the arch is well formed or high. When the muscles are relaxed and no weight is put upon the foot, the arch forms a gentle curve representing the anatomical resting position of the skeleton of the foot. When weight is put upon the foot with the muscles relaxed, the arch is depressed even in the normal foot. Thus, changeability, mobility or suppleness, is a feature of the normal arch, and a high arch which cannot flatten is as abnormal as a low arch which cannot be raised.

Pes cavus may, therefore, be defined as a high arch which is fixed, and the symptoms, when they arise, are due not so much to the shape of the foot, as to its lack of intrinsic mobility, its inability to " give " and adapt itself to varying circumstances. In other words, a high arch is abnormal when it ceases to be dynamic and becomes static.

An abnormally high arch is met with as an individual peculiarity in some people who at most complain of difficulty in finding ready-made boots and shoes that are comfortable. It is often associated with short broad hands.

It is said that in some cases a high arch is induced by crowding the feet of growing children into boots and shoes that are too small for them, and that the same effect is produced in women by short narrow shoes and high heels. But, with regard to the latter my experience is quite the reverse; such women nearly always have flat everted feet.

A certain amount of pes cavus is seen in cases of talipes equinus when the patient habitually walks on the toes with the heel off the ground. This occurs both in the normal foot, as when the equinus is merely compensatory for a shortened limb, and in cases of paralytic talipes equinus. In neither case as a rule is the cavus deformity a very prominent feature, and in both it is an almost wholly mechanical effect brought about by compression of the foot in its long axis by the body-weight, and secondary shortening of the soft parts in the sole.

A special place, however, has been given to the slighter degrees of talipes equinus—the so-called right-angled contraction of the tendo Achillis—in which the heel is not permanently raised off the ground. In fact, cases of pes cavus have been divided into two groups—those in which dorsiflexion of the foot is limited, and those in which it is not. Here again my experience is that this condition (right-angled contraction) is far more often associated

with flat foot than with pes cavus, and while not denying that some contracture of the sole may occur with the slighter degrees of talipes equinus as well as with the more severe, I would disagree with the view that contraction of the tendo Achillis is particularly associated with the severer grades of pes cavus. In the majority of cases exactly the opposite condition is present—that is, the foot is dorsiflexed at the ankle-joint, while the anterior part of the foot is plantarflexed at the mediotarsal joint. The plantarflexion of the fore part of the foot masks the dorsiflexion at the ankle-joint, and it has been erroneously assumed that because the toes cannot be raised above the level of the heel, the tendo Achillis must be contracted.

Pes cavus then may be associated with other deformities of the foot, but, apart from these there remains a well-defined group of cases in which increase of the arch is the essential condition, and this constitutes pes cavus proper.

The usually accepted explanation of this deformity is that which was given by Duchenne of Boulogne, who attributed it to paralysis of the interossei and lumbricals and of the abductor and flexor brevis hallucis. These muscles flex the toes at the metatarso-phalangeal joints and extend them at the inter-phalangeal joints, so that, when they are paralysed, the toes become hyper-extended at the former and flexed at the latter by the unopposed or uncorrected action of the long extensors and flexors. The proximal phalanges then come to occupy an almost vertical position, and the heads of the metatarsal bones are depressed. Continued action of the long extensors and flexors draws the toes backwards towards the heel, so that the arch of the foot is abnormally increased, and this becomes fixed by contracture of all the soft parts in the sole of the foot. As the anterior part of the foot becomes depressed in relation to the heel, the patient dorsiflexes the foot at the ankle-joint more and more in order to bring the heel to the ground. But if the deformity progresses beyond the point at which full dorsiflexion of the ankle-joint is reached, the anterior part of the foot then falls below the level to which it is possible to bring the heel, and the patient walks on his toes.

Cases are frequently met with in which there are obvious signs of residual paralysis from a preceding acute poliomyelitis. Pes cavus has also been recorded in cases of injury to the posterior tibial nerve. But, there are many more cases in which it is not possible to demonstrate any paralysis of the muscles, and in which there is no history of paralysis nor indeed of any illness preceding the development of the deformity. It has been suggested that in these cases the paralysis is so slight that it cannot be detected or it is overlooked. But I cannot think that it is right to invent a purely imaginary illness in order to provide a convenient ætiology for pes cavus. Moreover, there are other features of the deformity which make such an explanation most unlikely.

Pes cavus without evidence of paralysis is quite a characteristic deformity. It is bilateral and it makes its appearance as a rule in the latter part of childhood, usually about the age of seven to ten, when without apparent cause the sole of the foot becomes slightly hollowed out and the toes show a tendency to become clawed. The deformity slowly, but surely, increases, the sole becoming more and more concave, and the dorsum of the foot unduly prominent and convex, while the toes are strongly hyper-extended at the metatarso-phalangeal joints and flexed at the interphalangeal joints. The weight of the body is then borne entirely on the heel and the heads of the metatarsal bones, the latter forming a prominent " ball " of the foot. Painful corns and callosities are common beneath the heads of the metatarsals and over the proximal interphalangeal joints, where they press

against the boot. The gait is awkward, stumpy and inelastic, and the patient may suffer much from the painful callosities and corns. Voluntary movements of the foot and toes appear to be normal except in so far as they are limited by the fixed deformity. No evidence of actual paralysis can be found clinically, though it must be admitted that isolated paralysis of the small muscles is difficult, if not impossible, to demonstrate in a contracted foot.

This deformity then comes on gradually and without apparent cause at a more or less definite age. It is in many cases hereditary, and several members of the same family may be affected. When two or more children in a family are affected, they do not develop the deformity simultaneously, but each child begins to show signs of it as he reaches the characteristic age of onset.

These features strongly suggest some congenital defect, rather than an accidental infection, as the underlying cause of pes cavus. It is perhaps significant that some of the most typical examples of this deformity occur in association with Friedreich's ataxy—a condition which is itself hereditary and familial and which is generally considered to be of developmental origin. It should be specially noted that none of the characteristic spinal cord degenerations of Friedreich's ataxy is responsible for a peripheral paralysis such as could give rise to pes cavus, and that the clinical picture is that of associated developmental defects, rather than one of primary cord disease leading to secondary paralytic deformity.

The condition invites comparison with the atrophic claw hand which may be due to a cervical rib. In this case a congenital anomaly lies latent until adolescent or adult age, when the altered relationship between the rib and the surrounding parts gradually causes pressure on the lower roots of the brachial plexus, with consequent atrophy of the intrinsic muscles of the hand. Even more suggestive is the fact that a similar paralysis may occasionally be brought about by pressure between the brachial plexus and a normally situated first rib. Whether this is associated particularly with a postfixed plexus, I do not know; but clearly there must be some developmental fault in the relationship of the plexus to the rib.

During childhood a very considerable alteration occurs in the relations between the spinal cord and the vertebral column. Extending originally the whole length of the spinal canal, the cord at birth ends opposite the body of the third lumbar vertebra, while in the adult it reaches only to the lower border of the body of the first lumbar vertebra or the upper border of the second. In this process of relative shortening the lumbosacral nerve roots become drawn out and obliquely placed between their attachments to the cord and their exit from the vertebral foramina. Variations in the position and constitution of the lumbosacral plexus are frequent and are commonly associated with variations in the vertebral column. It is not difficult to imagine that slight developmental defects in the lumbosacral region of the spine or in the costal elements of the sacrum might give rise to pressure on the roots of the sacral plexus comparable to that which occasionally occurs in the cervical region. These considerations have led one to search for evidence of developmental anomalies in the neighbourhood of the first sacral nerve roots in cases of pes cavus, both with and without Friedreich's ataxy.

Naturally one looks first for radiographic evidence, and many cases of apparent defects have been noted in these cases, *e.g.*, spina bifida occulta, sacralisation or partial sacralisation of the fifth lumbar vertebra, while others again were apparently normal. But, the radiographic appearances in this

region are so variable and such fanciful interpretations have sometimes been given to them, that one hesitates to draw any conclusions from these cases.

In three cases I have explored the region of the first sacral roots. In one case there was a defect in the lamina of the fifth lumbar vertebra, in another the first sacral roots appeared to be smaller than normal, while in the third there was a definite thickening of the dura mater at the level of the fifth lumbar and first sacral vertebræ. It has not, however, been possible to draw any definite conclusions from these cases and I have had no opportunity of examining a case of pes cavus post mortem.

Treatment.

The treatment of the deformity of pes cavus has been much simplified by the introduction of Steindler's operation of " stripping the os calcis." Formerly, these cases were treated by subcutaneous division of the contracted fascia in the sole, and wrenching and manipulations and splints, and while there is no doubt that the deformity in most cases was corrected by these means, the general experience was that they showed a very great tendency to relapse. Steindler's operation aims at detaching all the soft parts from the posterior pillar of the arch of the foot, namely, the os calcis, so that when the foot is straightened, they slide forward and gain a new attachment further forward. This principle of shifting the attachments of contracted soft parts, rather than dividing them in the middle and allowing them to heal by scar tissue, is a great advance in the correction of deformity, and cases so treated do not show nearly the same tendency to relapse. Pes cavus therefore can in most cases be corrected without difficulty, and the comfort of the patient is greatly increased thereby.

THE INCIDENCE OF RICKETS
in a London Hospital Out-patient Department

BY

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There is wide difference of opinion as to the prevalence of rickets among the urban child population of Great Britain. This is, in part, attributable to the divergent standards of diagnosis accepted by various clinicians; on the one hand rickets is frequently diagnosed because the child has sweating of the head or flabby muscles or is backward without any evidence of pathological change in the bones, and on the other, some practitioners are not prepared to diagnose rickets until there is gross bone deformity.

Nature of the Investigation.

At the request of the Medical Research Council a systematic examination of children under two years of age was undertaken at the Queen's Hospital for Children in April, 1925, with a view to ascertaining the frequency of rickets among children of the out-patient class in the East End of London. The incidence of rickets is at its height at this season. It should be borne in mind that this hospital serves a large district, parts of which are among the poorest in London. In order to obtain uniformity, the findings were based on radiographic evidence, which is much less subjective than clinical signs. The wrist only was photographed for economy of time and material. Radiographic changes appear early in this situation, but it was recognised that by taking only the lower ends of the ulna and radius, the earliest signs of rickets might sometimes be missed, since the rapidly growing lower end of the femur may show changes before the radius and ulna. Radiographic diagnosis was based on fraying or blurring of the epiphysial margin, with or without cupping and evidence of osteoporosis.

The Children Examined.

During April, 1925, 169 children, aged from one week to two years, were examined at the Queen's Hospital for Children. The majority were new patients attending for the first time. No child who had attended for more than two to three weeks at the time of examination was included, on the ground that any case already diagnosed as rickets would have been treated, and there is no doubt that with treatment all radiographic signs rapidly disappear in the mildest cases. The children examined came from different departments of the hospital. Under 30 cases were medical out-patients. Over 100 were so-called casualty patients, *i.e.*, patients attending for treatment by the resident medical officers, many of them to be referred later to other hospital departments. Of these roughly rather more than half attended with " medical " complaints, for the most part minor

ailments such as constipation, " indigestion," bronchitis, etc., and the rest for surgical complaints or conditions affecting the skin, ears or eyes. About 30 more were either brothers or sisters of patients or were unselected children attending a neighbouring Welfare Centre who were included in order to increase the total number, since the investigation had to be completed within about three weeks and the work was simplified if the children were taken in batches. None of the Welfare Centre cases and only one of the relations of patients examined had radiographic evidence of rickets, so that among the hospital patients proper, the incidence was higher than the figures given below indicate.

The Incidence of Rickets as shown Radiographically.

The cases were unselected, except that two of the 169 children examined were sent to the hospital by practitioners for rickets. Excluding these, we have 167 cases, of which 13 showed definite evidence of rickets in the X-ray plate of the bones of the wrist, i.e., approximately 8% or 1 in 12. The total number of cases is much too small to determine age distribution, but it may be of interest to note that the youngest case radiographically diagnosed was four months old, and of the 13 cases of rickets (excluding the two sent to the hospital for rickets), six were under nine months of age, and 11 were under 13 months. Thus, if all children under four months or over 13 months are excluded from the total of 167, there are left 72 with 11 cases of rickets, or approximately 15%. It is, however, obvious that the numbers are insufficient to establish the percentage incidence at different ages. The majority were cases of very slight rickets—only one, a child of 18 months, could be classed as severe.

The belief appears to be general among clinicians that the incidence of rickets in London has greatly diminished during the last decade, and probably was steadily diminishing before that time. These figures, however, based on radiographic findings, are sufficient, in spite of the relatively small total numbers, to show that in poor districts it is still a formidable complaint. It must be remembered that rickets causes increased susceptibility to respiratory infections, and that these account every winter for a large seasonal rise in the infantile death rate, so that even slight cases of rickets cannot be dismissed lightly. Due allowance should be made for the fact that the majority of these cases were new hospital out-patients, and it is obvious that the incidence among the total population and even among those who have attended hospital for some months would be much lower. Even among out-patients, it has been demonstrated by another group of workers that the incidence is much less in patients drawn from a neighbourhood where the standard of living is higher than it is around the Queen's Hospital for Children, which draws its patients largely from poor and over-crowded boroughs such as Shoreditch, Bethnal Green and Hackney.

The Clinical Findings.

Each child was examined clinically by one of three observers before it was sent for radiographic examination. The standards adopted differed widely, in spite of an attempt at the outset to co-ordinate the scheme of notation of rachitic signs, and showed the futility of attempting to combine the clinical findings of observers who had not had ample time and opportunity to correlate their system of notation.

The clinical diagnosis is discussed separately.

The Eruption of Teeth.

The date of eruption of teeth in the 15 rachitic children was not noticeably delayed as compared with the non-rachitic ones. Cases of late dentition occurred in both groups, and the number of rachitic children is not sufficiently large for any valuable comparison to be made.

The Influence of Feeding.

As regards feeding: of the six rachitic children under nine months of age, four were at the time of examination artificially fed, one was entirely, and one partially, breast fed—findings which agree with the well known fact that artificially fed infants are more liable to rickets than breast fed. Of the children under nine months of age without radiographic evidence of rickets more than two-thirds were breast fed.

Summary.

One hundred and sixty-nine children were examined radiographically and clinically for evidence of rickets at the Queen's Hospital for Children in April, 1925. The hospital serves poor districts in the East End of London. The differing standards of the investigators invalidated the clinical findings in spite of an attempt at the outset to establish a common standard. The findings are, therefore, entirely based on the much less subjective radiographic diagnoses. Two rachitic children were excluded since they were sent to the hospital for that disease. Of the 167 remaining, 13 had radiographic evidence of rickets (*i.e.*, 8%), but if only infants between the ages of four and 13 months are considered, 72 cases are left, 11 of whom had rickets (*i.e.*, an incidence of about 15%). It should be remembered that the seasonal incidence of rickets is probably at its highest in April—the month chosen for the investigation—but the incidence is sufficiently high to indicate the necessity of a more vigorous effort on the part of the medical profession and the public to eliminate this disease—a result within our power if full use were made of the knowledge already in our possession. The vast majority of mothers are now aware of the desirability of an addition of fruit juice to the diet of an artificially fed infant. They require education in the necessity of as much outdoor life as possible, even when the weather is inclement, and the need of regular administration of cod liver oil all through the winter. It seems a pity that, when a valuable anti-rachitic such as cod liver oil is available, the public should spend such vast sums yearly on widely advertised substitutes—proprietary preparations of much less anti-rachitic value.

The cost to the hospital of the X-ray films was defrayed by the Medical Research Council at whose request the investigation was undertaken. The taking of the X-ray photographs was done by Sister F. Francis, to whom we are greatly indebted for undertaking this exacting piece of work in addition to all her routine work.

A NOTE ON THE CLINICAL DIAGNOSIS OF RICKETS IN INFANCY.

BY

HELEN MACKAY, M.D., M.R.C.P.

The diagnosis of rickets may be based on any one of the following: (1) Examination of the blood, *i.e.*, estimation of the blood phosphorus and blood calcium; (2) histological or (3) radiographic examination of the bones; (4) clinical examination of the patient.

It would seem probable that defective laying down of calcium in the growing bones results from an upset in the balance and the absolute amounts of the calcium and phosphorus salts in the blood, so that presumably the earliest diagnosis will in the future be based on blood examination and not on the secondary changes in the bones. Howland and Kramer claim that if the calcium concentration multiplied by the phosphorus concentration in milligrams per 100 cc. is less than 30, there is always rickets present, that if this figure is between 30 and 40 the rickets is slight or healing. In the present stage of our knowledge, however, the generally accepted criterion of rickets is the histological one, *i.e.*, the presence of excessive osteoid tissue, irregularity of the columns of cartilage cells, disorganisation at the epiphysial line and other pathological changes in the growing bones. As the bones, however, cannot be examined histologically during life, we are usually dependent on the evidence of changes revealed either by radiographic or by clinical examination—and these must of necessity be grosser and later manifestations of the disease than those revealed by microscopic examination.

During the course of the investigation into infantile rickets carried out in Vienna under the auspices of the Medical Research Council and the Lister Institute of Preventive Medicine in the early post-war years, the writer undertook daily examinations of infants with the object of observing and recording the development of rachitic signs.

As regards the *clinical diagnosis*, it is now established that no reliance can be placed upon such *general signs* as pallor, sweating, flabbiness of muscles or large abdomen. All these may appear in many different conditions of ill-health, and moreover, the general health may be actually improving at the time that bone changes are becoming manifest. The diagnosis must, therefore, be based on evidence of bone changes alone, and, in the opinion of the writer, the most important of these for early diagnosis of infantile rickets are an enlarged rosary and craniotabes. *Craniotabes* is much more common in an infant developing rickets at four, five, or six months old than in one in whom the disease does not make its appearance until after say seven months, since the rate of growth of the skull diminishes rapidly. Craniotabes may be defined as softening of the cranial bones which develops after birth, and must always be distinguished from congenital softness of the bones—often a difficult matter. Two points of value in the differential diagnosis are that (1) craniotabes is usually asymmetrical, congenital softness symmetrical, (2) craniotabes usually first makes its appearance behind the ears about the anterior ends of the occipito-parietal suture, congenital softness, if present at all, is usually well marked over the vertex, particularly about the posterior fontanelle. Craniotabes can be found in London infants with moderate frequency if it is systematically looked for, but its significance for

the diagnosis of rickets is far more widely recognised on the Continent than in this country. (The grounds for considering craniotabes a rachitic manifestation are set out elsewhere. *See* Studies of Rickets in Vienna, 1919-1922. Medical Research Council Special Report Series, No. 77, p. 130.)

The presence of a pathologically *enlarged rosary* must be determined by palpation—no measurement can be given to divide the normal from the pathological, and each observer must learn for himself what are the limits of the normal. Moreover, an enlarged rosary like enlarged epiphyses is present both in rickets and scurvy.

During the Viennese investigation, the writer with Dr. E. Dalyell examined daily in the post mortem room the bodies of infants under 12 months of age, noting in each case the size of rosary, the presence or absence of craniotabes, size of epiphyses, etc. The diagnoses were then tested histologically. In 84 cases sections of the costo-chondral junctions were cut by Dr. Feller. Fourteen of the series showed a degree of bone change before autopsy held to justify a clinical diagnosis of rickets—of these 12 were histologically rachitic and two were cases of scurvy. Of the remaining 70 in the series, 13 were histologically rachitic though no definite signs of the condition were found in the bodies before autopsy. The system of notation for the rosary was 0, $\frac{1}{2}$, $\frac{1}{2}$-1, 1, 1-1$\frac{1}{2}$, 1$\frac{1}{2}$, etc. It was found that many infants with a rosary of 1$\frac{1}{2}$ or more had other clinical evidence of rickets so that there was no doubt of the correctness of the diagnosis, and, therefore, only eight with beading of this grade were examined histologically. Of the eight, six were histologically rickets and the remaining two scurvy. Seven cases with craniotabes were examined and all had histological evidence of rickets. By frequent examinations of living children it was established that, taking craniotabes and a rosary of grade 1$\frac{1}{2}$ upwards as evidence of rickets, the clinical diagnosis could frequently be made in infants before there were any radiographic signs of the disease. When it is remembered that rachitic changes tend to develop first at those sites where there is most rapid bone growth, and that in young infants the skull bones and the ribs are growing much more rapidly than the limb bones (*i.e.*, those used for radiographic diagnosis for reasons of photographic technique), it is not surprising that an enlarged rosary or craniotabes can often be detected before there is evidence of rachitic change in the lower end of the radius and ulna.

As regards *other clinical sign sof rickets in infants* :—Bossing of the head, unless it is well marked, is difficult to diagnose with certainty on account of the wide normal variations in the shape of the head, and is, therefore, only occasionally helpful for early diagnosis.

Enlargement of the wrist is usually a somewhat later sign than enlargement of the costo-chondral junctions, and one must also bear in mind that there occurs normally between eight and 12 months of age an increase in prominence at the wrist which is sometimes mistaken for rachitic enlargement. By the time there is definite clinical enlargement of the wrist there is usually also radiographic evidence of the disease.

Bending of the limb bones is a relatively late sign and the degree of normal curvature of the tibia varies considerably so that a normal curve is frequently mistaken for a pathological one. A slight grade of thoracic deformity is often a fairly early sign, but this alone is insufficient for a diagnosis of rickets, since this deformity may arise in any young infant as a result, for example, of some respiratory embarrassment or persistent abdominal distension, though more likely to develop in a rachitic infant.

In the course of the *present investigation* at the Queen's Hospital for Children, which is described in the previous paper, all three observers have based their clinical diagnosis on evidence of changes in the bones, but many cases have been passed by W.K. and H.S. as normal, which would have been classed by H.M. as rachitic taking so far as possible the standard test by histological investigtion in Vienna. Definite craniotabes or a rosary of $1\frac{1}{2}$, with or without enlarged epiphyses, cranial bossing or thoracic deformity, was regarded as evidence of rickets.

There is no doubt, in the opinion of the writer, that the incidence of very slight grades of rickets is very much higher than the figures based on radiographic diagnosis would indicate. In the group of children examined by her at the Queen's Hospital for Children, 12 had clinical signs of rickets, though only five of them had definite radiographic evidence of the disease and in a sixth the evidence was doubtful. Every child in this group with radiographic signs of rickets had already been diagnosed clinically. The number showing histological changes indicative of the disease would undoubtedly be still larger.

Although clinical diagnosis can be made early it will always be subjective as it is not possible to convey in words the degree of beading or of epiphysial enlargement which is pathological: for example, prominence at the wrist which is within normal limits at one year would be pathological at five months, hence the very wide discrepancies in clinical diagnosis.

The only clinical sign which can be accepted as evidence of *active rickets* is persisting craniotabes. This disappears within a few weeks when the normal process of calcium metabolism is re-established, but enlarged epiphyses may remain for years and bent bones for a life time. A single X-ray plate, on the other hand, will often determine whether the disease is active, healing or healed.

Conclusions.

The writer's conclusions are as follows:—For early diagnosis in the future reliance is likely to be placed on the results of blood examination. Clinical diagnosis, based on bone changes (*e.g.*, an enlarged rosary, and in the young infant craniotabes), can be made early, and radiographic signs are usually somewhat later than the earliest clinical signs. An enlarged rosary and large epiphyses may, however, be signs of scurvy. Unless there is craniotabes present, the stage of the disease cannot be determined by a single clinical examination, but can frequently be settled by examination of a single X-ray plate; and radiographic diagnosis is much less subjective than the clinical. There is no doubt that the true incidence of rickets is higher than figures based on radiographic examination alone would indicate. How much higher it is impossible to say, but in the writer's opinion it is probable that perhaps twice as many cases of rickets might be detected by clinical examination as can be revealed radiographically, but this statement is based on impression and has not been tested on any large number of cases. Had it not been for the opportunity in Vienna, already mentioned, of comparing clinical and histological findings, the writer would have passed as normal many infants which, in the light of this experience, she would now class as very early rachitic cases.

A STUDY OF RICKETS; Incidence in London.

BY

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AND

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In order to ascertain the incidence of rickets in London a study was attempted during the months of February, March and April of 1925.

It was thought that these being the darkest months of the year, following on a long, sunless period, the incidence of rickets would be at its height.

Our first difficulty was to define the basis upon which rickets could be diagnosed. We had over and over again diagnosed rickets clinically because of a bossed skull, enlargement of ends of long bones and beaded ribs, only to find by X-ray that the rickets was completely healed. Clinically, therefore, it would only appear possible to diagnose that the child had had rickets, and it appeared impossible to us to diagnose the presence of active rickets with any degree of certainty by clinical methods. Since it was active rickets in which we were interested we were driven to study our cases with the radiographer, and X-rays of the wrists were taken in every case by Dr. Bertram Shires.

In all some 339 new cases were radiographed. The children's ages ranged from a few weeks to two years. This figure represents the total number of children of that age seeking advice at the Infants' Hospital and at St. Thomas' Hospital during that period.

Number of Cases of Active Rickets.

Out of 339 cases :—

4 showed active radiographic rickets—that is 1·2% of the total;

110 showed slight or gross signs of rickets clinically, but proved healed radiographically—that is 32% of the total;

225 appeared normal clinically and radiographically—that is 67% of the total were normal.

The Relationship between Cod-liver Oil and Rickets.

Probably the most surprising point elicited by this investigation was the fact that out of the 339 cases, 313 or 92% had been having some cod-liver oil preparation for a considerable period. That such a high percentage of the infants of the poor are receiving cod-liver oil should be a gratifying fact to those interested in public welfare. That these infants had been protected from rickets by this antirachitic medication there would seem to be very little doubt. None of the four cases of acute rickets had had cod-liver oil.

Of the 110 clinical rickets which were healed, 96 or 88% had had cod-liver oil. It is, therefore, safe to assume that the oil brought about healing in the darkest months of the year.

Of the 225 cases showing no clinical rickets, 216 or 96% had had cod-liver oil, and of the remaining nine cases five were entirely breast fed, one was partly breast fed and three had been entirely breast fed until just prior to the investigation.

Relationship between Diet and Rickets.

Of the four cases of active rickets, three were having whole full cream dried milk and since they were over a year old their diet was mixed consisting of cereals, gravy and potato; the fourth case had had cow's milk and cereals.

Of the 110 showing clinical rickets :—

36 or 33% had dried milk;
23 or 20% had sweetened condensed milk;
40 or 37% had cow's milk;
11 or 10% were on the breast.

The diets of those cases not showing clinical rickets were made up in much the same proportions :—

71 or 31% had dried milk;
29 or 13% had sweetened condensed milk;
79 or 35% had cow's milk;
46 or 21% had breast milk.

These figures suggest that despite the variety of diets as shown above the addition of cod-liver oil protects against rickets.

Relationship between Poverty and Rickets.

Does this relationship exist?

Does an infant develop rickets more readily in those homes which are poorest? Our statistics show the following :—

One case of active rickets came from a family consisting of parents and three children where the income was £5 per week.

Two cases of active rickets came from families where there were more than three children and the total earnings were £2 10s. 0d. per week.

The fourth case of active rickets came from a family where there were seven children with an income of £3 10s. 0d. per week.

These figures are too small to reach any conclusions of value, but it may be readily seen that in three of the four cases the families were poor.

Relationship between Weight and Rickets.

Of the 339 cases :—

45 or 13% were average weight;
10 or 3% were overweight;
284 or 84% were underweight;
The 4 acute rickets were all underweight.

Of the 110 clinical rickets :—

16 or 15% were average weight;
4 or 3% were overweight;
90 or 82% were underweight.

These figures show that the majority of the cases investigated were underweight. This series is too small from which to draw any conclusions of real value, but they seem to suggest that there is a relation between rickets and underweight.

Relationship between Dentition and Rickets.

Of the 110 clinical rickets :—

One-third were under the age of six months and therefore could not be expected to have teeth ;

And of the remaining two-thirds 44 or 63% showed delayed dentition calculated by text-book standards.

Of the four acute rickets, all showed grossly delayed dentition.

Of the remaining 225 not showing clinical rickets 71 were under six months, and of the 154 others, 81 or 53% showed delayed dentition when calculated in the same manner.

These figures suggest that if delayed dentition be due to rickets then a large proportion of our cases which appeared clinically and radiographically free from this condition must nevertheless have suffered from it. The alternative is that our standards for estimating the dentition of children of this class must be altered.

Conclusions.

1. In a series of 339 cases between birth and two years, there were four cases of active X-ray rickets—this is 1·2% of the total. Active rickets would appear to be uncommon at least in certain areas in London.

2. One hundred and ten cases showed clinical rickets which were proved to be healed, showing that 32% of our series had had rickets.

3. Ninety-two per cent. of the total series were having some cod-liver oil preparation.

4. Evidence is produced which suggests that cod-liver oil protected some from rickets, and healed rickets in other cases.

5. The diet of the normal cases showed that three-tenths were fed on dried milk, four-tenths on cow's milk, one-tenth on sweetened condensed milk and two-tenths on breast milk. Ninety-six per cent. of these however were having cod-liver oil, and the 4% remaining were breast fed.

6. According to modern standards 63% of cases with healed rickets and 53% of those cases not showing rickets clinically or radiographically had delayed dentition. This suggests to us that the average child of this class does not cut its first tooth at six months and new standards must be evolved for judging the state of dentition in hospital patients.

We must thank Dr. Bertram Shires for giving his time and help and enabling us to obtain the X-rays, and to the Medical Research Council we owe our thanks for the grant which covered the expenses involved in this investigation.

Recent Advances in the Diagnosis and Treatment of PURPURA HÆMORRHAGICA

BY

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The introduction of splenectomy in the treatment of purpura hæmorrhagica by Kaznelson[1] of Prague in 1916 marks one of the most striking advances in the therapy of blood diseases of recent years. Up to date more than sixty cases have been operated upon. The results are so uniformly good that it appears to be only a matter of time before the disease is classified as curable by splenectomy. The results are comparable with those of splenic anæmia and acholuric jaundice.

It is worthy of note that despite the widespread recognition of this form of treatment both on the Continent and in America the beneficial results are little known in this country. In Britain so far only two cases[27] have been recorded in which splenectomy was performed. Both gave encouraging results. That the disease is by no means common cannot be denied, but from the writer's own observations during the past two years it appears to exist in this country in about the same incidence as elsewhere. The purpose of the present article is to call attention to this excellent clinical field which is practically unexplored.

The number of published cases is now sufficiently great to admit of a short survey of the subject in the light of the results obtained. A review of the abstract of recorded cases brings out some very important features in the ætiology of the disease without, however, indicating the causal factor, which still remains obscure.

Results of Splenectomy.

This operation is almost uniformly successful in alleviating the symptoms. Further time must elapse, however, before we can definitely assert that the relief is permanent. The few cases which possess a post-operative period worthy of any consideration appear to hold out promise of success. In the first case operated upon, seven years have elapsed between the date of operation and the last report. During this period the patient has remained free from all signs and symptoms of the disease (Case No. 1).

TABLE I.

Splenectomy.	Results.		
No. of Cases.	Well.	Improved.	Died.
58	50	2	6

In the compiling of the various tables for statistical purposes only authenticated cases are considered. Reference to the abstract (*see* page 8) will find several cases in which the diagnosis of purpura hæmorrhagica cannot be admitted owing to the presence of other morbid processes. These cases

are examples of secondary purpura with hæmorrhages and as such are rightly excluded.

The results set out in Table I. are very striking in view of the severity of the disease, its hæmorrhagic nature and the considerable risk involved in the operation.

Under the category " Well " we find fifty cases. The average duration of the post-operative period of this group is just under two years. It will be understood that the term " well " is employed in the sense that the patient is enjoying an active life and is no longer subject to hæmorrhages. The occurrence of slight hæmorrhage during the convalescent period is discounted as of no moment. In the great majority of cases in this category the recovery is complete. In a few cases, however, the purpuric manifestations have persisted in a minor degree for some time after the operation. Kaznelson[2] states in reference to his last case " that the effect of the surgical treatment in this case was to transform purpura hæmorrhagica into purpura simplex."

Under the category " Improved " there are but two cases, and little information is available beyond the statement that the severity of the disease has been somewhat abated.

Mortality.

The present series of records includes six cases which terminated fatally; a mortality of 6 in 58.

At first sight this figure hardly appears to warrant an optimistic outlook for the new treatment. The mortality from the disease itself is probably little more than ten per cent., though it is difficult to assess any figure, for no reliable statistics exist. An analysis of the cases reveals interesting information.

As will be pointed out later, the diagnosis of the condition is only certain where the disease is chronic. Of the six fatal cases three only fulfil this proviso. Now of these three chronic cases the fatal result in two instances appears to be directly associated with the risks of operation and not with the disease itself. We are thus left with only a single instance of death following operation in an authentic case in a series of fifty-eight cases.

The following list of fatal cases is taken from the abstract :—

TABLE II.

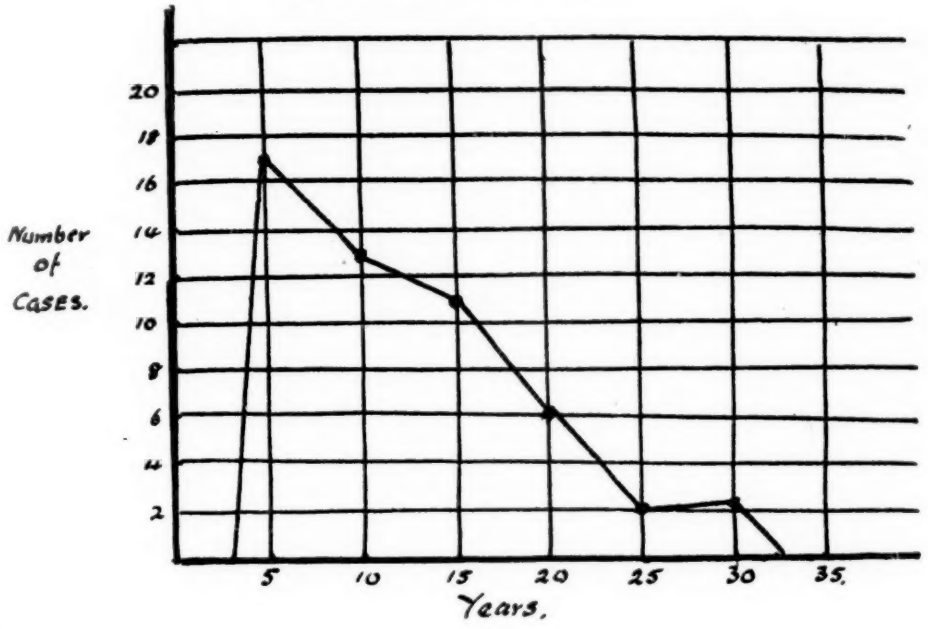
Case No.	Sex.	Age at onset.	Duration.	Main Site of Hæmorrhage.	Remarks.
3	F.	20	7/12 years	Nose	Myocardial hæmorrhage.
17	F.	9	12 years	Uterus	Subphrenic abscess on 29th day.
26	M.	29	4 days	Bowel	
34	F.	16	4 days	Uterus	
41	F.	12	4 years	Nose	Accident, hæmorrhage at operation. Death 6 hours post-operation.
65	M.	45	Very short		

Some Ætiological Factors.

Age at Onset.

The disease is essentially one of early youth. An analysis of the abstract clearly establishes this. In the youngest case recorded the onset of the disease occurred in the 3rd year. The commonest age for the disease to manifest itself is about the 5th year; thereafter it steadily declines up to the 15th year. Later the incidence of onset falls rapidly and the disease rarely commences after the age of thirty years.

Age at Onset in Sixty Cases.



Sex.

Another striking feature is the preponderance of the condition amongst females. Out of a total of fifty-eight authentic cases forty-four were females and fourteen males—a ratio greater than 3 to 1. Menstruation does not appear to be a deciding factor in the disparity of the incidences of the disease in the two sexes, for the preponderance is clearly established before the age of puberty.

Duration.

The longest duration of the disease recorded in the present series is thirty years.

In the majority of cases the condition appears to be chronic. The onset may be acute, but as a rule it is insidious. Remissions are a common feature in most cases. During the period of remission the patient may be free from all signs of a hæmorrhagic tendency. More commonly, however, there is only a cessation of external hæmorrhages, and usually one or more features of the condition persist in the skin and mucous membranes, *i.e.*, a state of purpura simplex is more or less persistent.

The blood changes which are so prominent a feature of the disease participate in these fluctuations.

The existence of an acute form of the condition is a matter of uncertainty. The evidence in support of such a type is extremely meagre. The only published record of cases with a single attack are those which have come to operation, and it is a moot point as to whether these cases would not have pursued the usual chronic course had they been left untreated.

Dr. G. A. Sutherland has informed the writer that he had met with cases in young subjects which presented all the clinical and blood features of purpura hæmorrhagica without a history of a previous attack. These cases have all recovered from their first attack unaided by treatment, apart from rest in bed. It will be of interest to note whether these subjects develop further attacks.

Forms of Hæmorrhage.

Hæmorrhage may occur in any part of the body. The nose and the uterus are the sites of major hæmorrhage and practically all cases fall into two groups :—

1. Those with epistaxis as the main feature.
2. Those in which uterine hæmorrhage predominates.

In females it appears to be the regular course for the disease to begin in childhood with recurrent epistaxis. Where this is mild no advice is sought. At the onset of menstruation epistaxis usually becomes less frequent and of minor import. The main site of hæmorrhage is then transferred to the uterus. Menorrhagia occurs and this, not infrequently, passes on to intractable metrorrhagia. This type of case constitutes the gravest form of the disease.

TABLE III.

Sites of Hæmorrhage.	Incidence in 54 Cases.
Gums	43
Nose	30
Uterus	24
Urinary Tract	2
Brain	2
Bowel	2
Skin :— Petechiæ and Ecchymoses	54

The minor hæmorrhages, petechiæ and ecchymoses, are present in all cases. Bleeding from the gum is so commonly found as to be of some diagnostic value. It consists of a continuous ooze from the crest of the gum which defies all local treatment, at times the loss of blood is severe and considerable.

Melæna is by no means an uncommon finding. This is usually due to swallowed blood from the nose and mouth, and rarely is it due to hæmorrhage from the bowel. Hæmorrhages from the bowel may, however, occur.

Several cases are recorded where intracranial hæmorrhage has occurred as manifested by temporary paralysis. A fatal case of intraventricular hæmorrhage is recorded by Pereyra[15].

Other less common sites are the urinary tract, joints, muscles and retina.

Diagnosis.

Prior to the work of Frank and Kaznelson the term purpura hæmorrhagica was applied with much ambiguity. A recapitulation of the various conditions which received the title of purpura hæmorrhagica would serve no useful purpose here other than to indicate the desirability of a recognised definition of the term.

Since the introduction of splenectomy as a form of treatment several new titles for the condition are found in the literature, such as thrombopenic purpura hæmorrhagica, essential thrombocytopenic purpura hæmorrhagica, and even essential thrombocytopenia. These titles have served a useful purpose in focussing the attention of clinicians on the necessity for an accurate diagnosis in view of the gravity of the operative treatment. With the increasing recognition of the disease the present tendency is to return to the original title of Werlhof, namely, purpura hæmorrhagica. He applied this to an idiopathic condition in which there were purpuric manifestations on the surfaces of the body accompanied by hæmorrhage from the mucous membranes. His definition holds good to-day so far as it goes, but now certain features in the blood must be essentially present before the term purpura hæmorrhagica is applied.

A survey of the published cases emphasises the necessity of a rigid acceptance of the modern interpretation of the term purpura hæmorrhagica before splenectomy is undertaken. To apply this method of treatment to cases which present other features in addition to those of purpura hæmorrhagica is to enter the field of experimentation, and it should be clearly recognised as such, lest the undoubted value of splenectomy in purpura hæmorrhagica be called into question.

Briefly the points of diagnosis are as follows :—

1. Purpuric manifestations in the skin and mucous membranes, *i.e.*, petechiæ and ecchymoses.
2. External hæmorrhage from the mucous membrane.
3. It is a primary disease.
4. There must be an entire absence of significant signs and symptoms apart from :—
   - (*a*) Those associated with hæmorrhage.
   - (*b*) The resultant anæmia, which is essentially of the chlorotic type.
   - (*c*) The enlargement of the spleen which may or may not be palpable.
5. It is a disease of early life running a chronic course.
6. Negative family history.
7. The blood shows the following features :—
   - (*a*) Considerable reduction in the number of blood-platelets.
   - (*b*) A non-retractile clot.
   - (*c*) Prolonged bleeding-time with a normal coagulation time.

It must be pointed out that the above changes in the blood are not solely confined to purpura hæmorrhagica. They may be present wholly or in part in other conditions. It is not uncommon to encounter them in the various blood dyscrasias such as pernicious anæmia and the leukæmias. Apart from blood diseases they are liable to be present in any condition complicated by a secondary purpuric eruption. They are, in fact, only of significance when they stand alone in a subject as a primary condition. Case No. 55 in the abstract provides valuable illustration of the relative unimportance of the blood changes *per se* in the diagnosis of purpura hæmorrhagica. This case presented a blood condition typical of purpura hæmorrhagica, *but in addition* the blood picture indicated a marked myelogenous and erythroblastic reaction in the bone marrow. This case terminated fatally. The diagnosis appears to be myelogenous leukæmia.

It is obvious from a study of the recorded cases that the greatest difficulty in diagnosis lies in discriminating between primary purpura hæmorrhagica and secondary purpura with hæmorrhages. Each case requires prolonged investigation before one can be reasonably certain that the hæmorrhagic features are primary and not secondary to other morbid processes. *In many cases time alone will reveal the true nature of the condition present.*

During the first attack of the disease it is quite impossible to be certain that the condition is not secondary. Where the onset of purpura hæmorrhagica is acute the clinical picture is very close to that of the hæmorrhagic forms of some of the exanthemata. Unfortunately the blood changes are common to both conditions and afford no guide to diagnosis.

The problem is clearly reflected by the results of operation in the so-called acute form of the disease. Three cases have come to operation within four days of the onset and all have ended fatally. At autopsy two showed no lesion to which the condition could be attributed, the third showed extensive tuberculosis. Against these we can find only one case operated upon during the first attack which recovered. The inference is clear—operation during the first attack of the disease is strongly contraindicated both on account of the uncertainty of diagnosis at this stage of the disease and because of the unfavourable results recorded.

The paucity of recorded cases treated by operation in this country seems to indicate that the disease is not being recognised. Contrary to the general conception, the disease, in the majority of instances, is not very evident at first sight. The skin manifestations are not as a rule very intense, in many cases they consist of a few scattered petechiæ in the region of the upper thorax and neck. The sites of any constricting band such as the collar and waist-band, may exhibit a few pin-point hæmorrhages under the skin. Their presence should excite suspicion and a careful and complete physical examination with serious enquiry into the past history may lead to the recognition of the obscure cases.

Enquiry into those anomalous cases of recurring epistaxis which not infrequently present themselves at casualty departments would undoubtedly lead to a more frequent recognition of the condition.

Another class of case which could be readily missed is the one which comes to the gynæcologist for severe menorrhagia or metrorrhagia. Almost half the number of cases which have come to operation are of this class. Where the female subject has reached the age of puberty uterine hæmorrhage is the classical form of the disease. All cases of intractable uterine hæmorrhage not due to a local cause should be subjected to a complete

physical examination. The features in the blood characteristic of purpura hæmorrhagica should be looked for, and the past history carefully studied.

A third source of enquiry lies in those cases of so-called atypical hæmophilia. The diagnosis of hæmophilia is often too readily made despite the absence of some of the main features of the condition. Where the clinical picture does not conform to the requirements laid down by Bulloch and Fildes[38] in their classical monograph the diagnosis of hæmophilia may be viewed with suspicion. The existence of hæmophilia in females has never been accepted notwithstanding several reported cases. A negative family history in any case exhibiting a hæmorrhagic diathesis strongly suggests the possibility of the case being one of purpura hæmorrhagica.

The writer has met one case which for eight years was considered one of hæmophilia despite a completely negative family history. Complete investigation revealed a perfect example of purpura hæmorrhagica.

Happily the two conditions are readily distinguishable notwithstanding a superficial resemblance to each other. The points in the differential diagnosis are as follows :—

	Purpura Hæmorrhagica.	Hæmophilia.
Sex	Either	Males only
Family History ...	Negative	Positive
Coagulation Time...	Normal	Prolonged
Bleeding Time ...	Prolonged	Normal
Blood Platelets ...	Diminished	Normal
Clot Retraction ...	Absent	Normal

Conclusions.

A study of the published cases of purpura hæmorrhagica treated by splenectomy justifies the acceptance of this method of treatment. But excellent as are the results of spenectomy, each case requires to be considered on its own merits. Where the disease is mild and causes no great inconvenience to the patient, splenectomy is not justified.

The operation should be reserved for chronic cases which fall into two groups :—

(i.) Where chronicity with severity so interferes with the normal life of the subject that a state of chronic invalidism is established.

(ii.) Where the severity of the hæmorrhages and the frequency of its occurrence constitute a real danger to the life of the patient.

ABSTRACT.

No.	Year.	Author.	Sex.	Age at onset.	Duration.	Family History.	BLOOD.				HÆMORRHAGES.							Main site of Hæmorrhage.	Splenomegaly.	Splenectomy.	Time since operation.	Result.	Remarks.
							Platelets.	Bleeding Time.	Coagulation Time.	Clot.	Petechiæ.	Ecchymoses.	Nasal.	Uterine.	Gums.	Gut.	Urine.						
1	1916	Kaznelson	F	5	30 yrs.	Neg.	200	+	—	*Non-retract	+	+	+	+	+	—	—	Uterus	+	+	7 yrs.	Well	*Non-retractile clot.
2		,, ...	F	20	27 ,,	,,	500	+		N-R	+	+	+	+	—	+	—	Uterus	+	+	7 ,,	,,	
3		,, ...	F	20	7/12 yr.	,,	1,800	+		N-R	+	+	+				—	Nose	—	+		Death	Myocard. hæmorrh.
4	1917	Benecke	F	15	5 yrs.	,,	66,000	+		N-R	+		+				—	Uterus		+	5 ,,	Well	
5		Schmidt			1 yr.	,,	Diminished			N-R	+	+	+		+			Nose	+	+	6 ,,	,,	
6		,, ...		9	2 yrs.	,,	,,		—	N-R	+	+	+		+			Nose	+	+	6 ,,	,,	
7	1919	Minkowsky	M	30	Many	,,	29,000	19 min.	—	N-R	+	+	+	—	+	—	—	Nose		+	5 ,,	,,	
8	1920	Ehrenberg	F	15	3 yrs.	,,	Nil.	+	—	N-R	+	+	+	+	+			Uterus		+	5 ,,	,,	
9		Minot	F	10	10 ,,	,,	10,000	+	—	N-R	+	+	+	—	+	—	—	Nose		+	2½ ,,	,,	
10		Herfarth	M	7	12 ,,	,,	8,000	23 min.	—	N-R	+	+	+	—	+	—	—	Nose	—	+	2 ,,	,,	
11		,, ...	F	8	12+	,,	30,000	+	—	N-R	+	+	+	+				Ut. & N.	—	+	1 yr.	,,	
12		Keismann	F	13	4 yrs.	,,	45,000	+	—	N-R	+	+	+	+	+	+	—	Gut		+	3 yrs.	Improved	
13	1921	Retzlaff																		+		Well	No record of details.
14		Kaznelson	F	5	25 ,,	,,	1,300	+	—	N-R	+	+	+	+	+	—	—	Uterus	+	+	3 ,,	,,	
15		,, ...	F	8	3 ,,	,,	600	+	—	N-R	+	+	+	—	+	+	—	Nose		+	3 ,,	,,	
16	1922	Cori	F	10	Many	,,	2,000	+	—	N-R	+	+	+	—	+			Nose	+	+	3 ,,	,,	
17		,, ...	F	9	12 yrs.	,	27,000	+	—	N-R	+	+	+	+	+	—	—	Uterus	+	+	29 days	Death	Subphrenic abscess.
18		Steinbrinck	F	3	2 ,,	,,	25,000	37 min.	—	N-R	+	+	+	—	+	+	—	Nose	—	+	2 yrs.	Well	
19		Bowen	M	4	18 ,,	,,	Few	20 ,,	—	N-R	+	+	+		+	+		Nose	—	+	4/12 yr.	,,	
20		Ricaldoni & Albo ..	F	18	3 ,,	,,	,,	30 ,,	—	N-R	+	+	+	+	+	—	+	Uterus	—	+	2/12 ,,	,,	
21		,, ,, ..	F	24	10+	,,	,,	+	—	N-R	+	+	+	+	+	—		Uterus	—	+	3/12 ,,	,,	

ABSTRACT—*continued.*

No.	Year.	Author.	Sex.	Age at onset.	Duration.	Family History.	BLOOD.				HÆMORRHAGES.							Main site of Hæmorrhage.	Splenomegaly.	Splenectomy.	Time since operation.	Result.	Remarks.
							Platelets.	Bleeding Time.	Coagulation Time.	Clot.	Petechiæ.	Ecchymoses.	Nasal.	Uterine	Gums.	Gut.	Urine.						
22		Pereyra					Diminished			N-R	+	+	+	—				Brain		—	—	Death	Intra-ventricular hæmorrhage.
23	1923	Brill & Rosenthal ...	F	5	14 yrs.	Neg.	6.000	+	—	N-R	+	+	+	—	+	+	+	Nose	—	+	2 yrs.	Well	
24		,, ,, ..	M	11	4 ,,	,,	Few	13 min.	—	N-R	+	+	+	—	+	—	—	Nose	+	+	2 ,,	,,	
25		Engel	F	12	10 ,,	,,	19.000	+	—	N-R	+	+	—	+	+		—	Uterus	—	+	6/12 yr.	,,	
26		,, ...	M	29	4 days	,,	Few	180 min.	—	N-R	+	+	—	—	+	+	—	Gut	—	+		Death	1st attack.
27		,, ...	M	44	2 days	,,	90.000	—	—		+	+	—	—	+	+	—	Gut	—	+		,,	1st attack. Extensive
28		Hitzrot	F	7	1 yr.	,,	40.000	20 min.	—	N-R	+	+	+	—	+	+	—	Nose	—	+	¾ ,,	Well	Tuberculosis at P.M.
29	1923	Cohen & Leman	M	5	1 ,,	,,	Few	5 min.	—		+	+							—	+	½ ,,	,,	
30		Bass & Cohen	F	5	3 yrs.	,,	11.000	20 min.	—	N-R	+	+	+					Nose	+	+	½ ,,	,,	
31		Giffen & Holloway ..	F	23	9 ,,	,,	22.000	120 min.	—		+	+	+	+	+			Uterus	—	—		Death	No operation.
32		Engel	F	17	1/12 yr.	,,	14,000	12 min.	—	N-R	+	+	+	+	+	+	—	Uterus	+	+	1 ,,	Well	
33		Wild	M	5	10 yrs.	,,	30.000	+	—	N-R	+	+	+	-	+	—	—	Nose	—	+	1 ,,	,,	
34		Herman	F	16	4 days	,,	Diminished	+	—	N-R	+	+	+	+	+	+	—	Uterus	—	+		Death	1st attack.
35		Vogel	M	5	7 yrs.	,,	25.000	90 min.	—	N-R	+	+	+	—	+	+	—	Nose	—	+	2 yrs.	Well	
36		,, ...	F	5	20 ,,	,,	Few	+	—	N-R	+	+	+	+	—	—	—	Uterus	—	+	2 ,,	,,	
37		Halban	F	15	2 ,,	,,	,,	17 min.	—	N-R	+	+	+	+	—	—	—	Uterus	—	+	1 yr.	,,	
38	1924	Sutherland & Williamson	M	10	6/12 yr.	,,	5.000	12 min.	—	N-R	+	+	+	—	+	+	—	Nose	+	+	1½ yrs.	,,	
39		,, ,,	F	5	3 yrs.	,,	15.000	10 min.	—	N-R	+	+	+	—	+	+	—	Nose	+	+	1½ ,,	,,	
40		,, ,,	F	4	8 ,,	,,	80.000	7 min.	—	?	+	+	+	—	+	—	—	Nose	—	—			No operation.
41		Meyerstein	F	12	4 ,,	,,	3.000	25 min.	—	N-R	+	+	+	—	-	—	—	Nose	—	+		Death	Accident at operation.
42	1923	Mayo Clinic	F	10	13 ,,	,,	40.000	+			+	+	+	+				Uterus	+	+	1 5/12 yr.	Well	
43	1924	,, ,, ...	M	12	12 ,,		Diminished				+	+	+		+			Nose	—	+	1 1/12 ,,	,,	

ABSTRACT –*continued.*

No.	Year.	Author.	Sex.	Age at onset.	Duration.	Family History.	BLOOD.				HÆMORRHAGES.							Main site of Hæmorrhage.	Splenomegaly.	Splenectomy.	Time since operation.	Result.	Remarks.
							Platelets.	Bleeding Time.	Coagulation Time.	Clot.	Petechiæ.	Ecchymoses	Nasal.	Uterine	Gums.	Gut.	Urine.						
44	1924	Clopton	M	5				13 min.												+	1 yr.	Well	No details available.
45		,, ...	F	5				37 min.												+	1 ,,	,,	,, ,,
46		,, ...	F	34																+		Improved	,, ,,
47		Vogel	M	10+																+		?	,, ,,
48		v.d. Wedt	F	30																+		Well	,, ,,
49		Brill	F	18	3/12 yr.	,,	10,000	+		N-R	+	+	+	—	+	+	+	Nose		+		,,	
50		Vincent	F	11	17 yrs.	,,	1,000	40 min.	—	N-R	+	+	+	+	+	—	—	Uterus	—	+	1 ,,	,,	Meningeal hæmorrhage.
51		,, ...	F	9½	4 ,,	,,	10,000	60 min.	—	N-R	+	+	+	+	+	—	—	Nose	+	+	1 ,,	,	
52		,, ...	F	9	5 ,,	,,	Few	45 min.	—	N-R	+	+	+	+				Uterus	—	+	1 ,,	,,	
53		,, ...	F	6	3/12 yr.	,,	,,	18 min.	—	N-R			+	+	+			Nose	—	+	⅓ ,,	,,	
54		,, ...	F	60	4 yrs.	,,	,,	10 min.	24 min.	N-R	+	+	+	—	—	—	—	Nose	+	+	¾ ,,	,,	Cirrhosis of liver.
55		Farley	F	18	2/12 yr.	,,	30,000	20 min.		N-R	+	+		+	+			Uterus	+	+		Death	Myelocytes; Normoblasts.
56	1923	Mayo Clinic	F	30	2 yrs.	,,	5,000	+		N-R	+	+	+	+	—	—	—	Uterus	+	+	2 yrs.	Well	
57	1924	,, ,, ...	F	6	5 ,,	,,	50,000	60 min.			+	+	+					Nose	+	+	1 yr.	,,	
58		,, ,, ...	M	30	2 ,,	,,	36,000	15 min.		N-R	+	+	+		+	+	+	Nose	+	+	½ ,,	,,	
59		,, ,, ...	F	6	5 ,,	,,	54,000	10 min.		N-R	+	+	+	+	+			Nose	+	+	½ ,,	,,	
60			F	5	10 ,,	,,	42,000	6 min.		N-R	+	+	+	+				Uterus	+	+	½ ,,	,,	
61		,, ,, ...	F	10—	10 ,,		42,000	+		N-R	+	+	+	+	+			Uterus	—	+	½ ,,	,,	
62	1925	,, ,, ...	M	27	1½ ,,	,,	52,000	20 min.	—	N-R	+	+	+		+			Nose	—	+	¼ ,,	,,	
63		Chauffard & Duval ..	F	5	10 ,,	,,	60,000	+	—	N-R	+	+	+	+	+	—	+	Uterus	+	+		,,	
64		Cowan	F	27	8 days	,,	Few	21 min.	—	N.R	+	+	+	+	+			Uterus	+	+	7/12 yr.	,,	1st attack.
65		Harttung	M	45			100,000	15 min.	—		+	+	+		+			Nose		+		Death	1st attack.

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KETONURIA AND URINARY ACIDITY

BY

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Introduction.

The significance of acetone bodies in the urine subsequent to surgical operations has long been the cause of controversy and is not as yet settled.

It is now well recognised that ketone bodies are not necessarily associated with acidosis. Although a ketosis usually accompanies an acidosis, the reverse is by no means the case. Despite the fact that a true acidosis—a depletion of the alkali reserve of the blood—is not necessarily indicated by ketonuria, the finding of acetone bodies in the urine following an operation, is still in clinical work frequently looked upon as a matter of much significance, especially in children. The estimation of the alkali reserve of the blood in the presence of an acid urine will, of course, at once decide whether a condition of acidosis be present or not. This, however, is rarely a possible procedure in practice and cannot always be undertaken even in a hospital. The clinical symptoms accompanying a definite case of acidosis also make this condition clear, but again, one would wish to have warning before the development of air hunger and collapse. Any information likely to be of assistance from a clinical point of view would be of advantage and any simple means of obtaining this, a help.

The acid-base equilibrium of the body is maintained by the kidneys as well as by the lungs. It is reasonable to suppose, then, that a consideration of urinary acidity would be of much value in dealing with patients exhibiting a ketosis. On this account an investigation has been carried out to determine how far post-operative ketosis, judged by the usual qualitative tests, is related to the acidity of the urine. It seemed probable that a simple method of estimating such acidity by means of indicators would be of value and give a better idea of the patient's condition than could be obtained by merely testing the urine for acetone bodies. The tests employed for this purpose are not only open to criticism (Bigwood and Ladd)[1], but, even in cases where acidosis is present, it has been shown that ketone bodies cannot be held responsible.[2] [3]

Methods.

Although the reaction of the urine varies to a considerable extent from time to time, in the normal condition the range lies between pH. 7·5—5·0. Unless the reaction lies below pH. 5·0, acidosis can be ruled out.

Brom-cresol-purple covers the usual range better than any other indicator, its range of reaction lying between pH. 6·8—5·2. On this account it is known that an acidosis can be excluded if a urine is alkaline to this indicator. At the same time, however, owing to the difficulty of reading the colours at either end of this range, and to a urine being at times much more acid or alkaline, brom-cresol-purple alone will not suffice in carrying out estimates of urinary pH.

Methyl red (pH. 6·0—4·6) was used for readings on the acid side, and phenol red (pH. 8·4—6·0) for those on the alkaline.

Five cc. of urine were measured into a tube and five drops of the indicator added. This was put in a comparator and read against Clark and Lubs standards made up with a similar mount of indicator. The standards were, of course, backed with tubes containing some of the urine being investigated. The urines were filtered where necessary and tubes of a like calibre used throughout.

The ferric chloride and Rothera's sodium nitroprusside tests were used to determine the presence of acetone bodies. The investigation was carried out upon the urines of children who had undergone tonsillectomy on the previous day and who subsequently developed ketosis. None of them developed abnormal symptoms. Controls were obtained by examining urines of children, mostly convalescent, in whom ketosis was absent.

It is realised that the reaction of the urine varies to some extent throughout the day, owing to the alkaline tide. The conditions under which the urine of post-operative cases and the controls were obtained were, however, comparable.

The patients undergoing the operations, and whose urine was subsequently investigated, were all otherwise healthy, and there is therefore no reason to suppose that there was any renal inefficiency which might prevent the output of acid salts.

TABLE I.

Cases exhibiting Marked Ketosis.

		pH.			pH.			pH.
1.	L.W.	5·9	11.	A.H.	5·5	21.	M.C.	5·5
2.	B.A.	6·0	12.	J.V.	5·4	22.	R.S.	6·0
3.	S.C.	5·7	13.	D.B.	5·6	23.	A.A.	5·8
4.	C.S.	6·2	14.	V.R.	5·3	24.	R.B.	5·8
5.	H.M.	6·2	15.	D.S.	5·6	25.	J.A.	5·5
6.	J.S.	5·6	16.	E.W.	5·6	26.	E.M.	5·4
7.	W.P.	5·7	17.	E.T.	5·7	27.	M.S.	5·5
8.	L.P.	5·6	18.	P.R.	5·9	28.	P.S.	5·8
9.	D.A.	5·6	19.	L.P.	5·6	29.	H.A.	6·2
10.	D.S.	5·6	20.	L.S.	6·0	30.	W.J.	5.8

Average: pH. 5·72.

TABLE II.

Cases exhibiting Ketosis, but to a less marked degree than the above.

		pH.			pH.			pH.
1.	C.M.	6·0	5.	H.B.	6·0	9.	R.L.	6·6
2.	L.K.	6·0	6.	M.H.	5·6	10.	J.M.	5·8
3.	S.W.	6·8	7.	F.D.	6·8	11.	D.U.	5·7
4.	D.V.	6·2	8.	J.W.	6·8	12.	Y.J.	6·2

Average: pH. 6·21.

TABLE III.

Controls—(Complete absence of Retosis.)

		pH.			pH.			pH.
1.	B.L.	7.0	11.	S.D.	6·4	21.	H.B.	6·4
2.	D.R.	5·8	12.	D.M.	5·5	22.	J.W.	6·8
3.	A.T.	6·4	13.	R.B.	6·0	23.	F.P.	7·4
4.	H.B.	6·4	14.	D.W.	5·8	24.	J.W.	5·2
5.	G.R.	5·8	15.	J.C.	6·6	25.	B.C.	5·6
6.	M.T.	7·0	16.	C.F.	5·8	26.	J.W.	5·5
7.	P.M.	7·2	17.	J.W.	6·8	27.	W.D.	6·8
8.	A.H.	6·2	18.	M.P.	6·9	28.	D.B.	6·8
9.	M.S.	6·2	19.	D.A.	7·0	29.	M.L.	6·8
10.	A.S.	6·4	20.	M.A.	6·6	30.	A.H.	6.0

Average: pH. 6·37.

Results and Discussions.

Table I. shows the urinary pH. of 30 cases, all of which exhibited marked ketosis as judged by the usual qualitative tests. The average acidity was pH. 5·72.

In Table II. is set out the pH. of urines in a series showing definite; but less marked ketosis. The average pH. was 6·21.

Table III. shows the reaction of the control urines in which the average pH. was 6·37.

Henderson and Palmer, who also carried out colorimetric determinations of urinary pH. in 1913, obtained an average of pH. 6·03 for normal urines.(4)

It will be seen that in no instance did the urinary pH. fall below 5·3 in the series given in Table I. That is to say, that the reaction lay approximately within normal limits and never approached a point indicative of acidosis.

It will be observed that the urines given in Table II. show hardly any difference in their acidity, though ketosis in them was much less marked.

An average urinary pH. of 6·37 was obtained in the control cases (Table III.). Ten of these 30, however, had urinary acidities ranging between pH. 6·0—5·2, despite the absence of ketosis. Conversely, it should be noted that of the total number of cases exhibiting ketosis (Tables I. and II.), in 15 the pH. lay between 6·0—6·8.

Although on the average the urinary acidity is greater in those cases where ketone bodies were present, the variation from the normal is slight. In no case, moreover, was a urine encountered where the urinary acidity approached a pH. indicative of an acidosis. This despite the fact that the tests for acetone bodies were strongly positive.

Unless a patient is passing at least 1 gm. of acetone bodies in the 24 hours the ketosis is unlikely to be serious *per se*. In the absence of any quantitative estimations the mere qualitative tests may well mean nothing, even if strongly positive.

It may be considered that apart from any question of acidosis, the ketone bodies themselves have a harmful effect. Provided, however, that the patient is devoid of clinical symptoms and the urinary reaction lies on the alkaline side of pH. 5·2 it seems unreasonable to regard post-operative occurrence of acetone bodies in urine with any anxiety whatever.

Although the estimations of urinary pH. were carried out for the purposes of this paper as described above, a sufficiently close indication of the acidity can be obtained without any special apparatus, simply by the use of indicators as follows :—

Take an inch of urine in a test tube. Add five drops of brom-cresol-purple (0·04% aqueous sol.). If the colour obtained is purplish, no further tests need be carried out. The pH. is on the alkaline side of 6·4.

If a yellow colour is obtained, add to a like quantity of urine in another tube, five drops of methyl red (0·02% in 60% alcoholic sol.). If the colour then obtained is yellowish orange and not a deep pink, the urinary acidity lies to the alkaline side of pH. 5·4 and no danger from an acidosis need be feared.

In the above work it was found that these two indicators were for practical purposes satisfactory for the range with which one is likely to be concerned.

Summary and Conclusions.

1. Qualitative tests for acetone bodies give but a rough measure of the degree of ketonuria present and should not be regarded as necessarily any evidence of acidosis.

2. The average urinary pH. of 42 cases exhibiting ketosis was 5·86, while that of the controls was 6·37.

3. In none of the above cases of ketosis following tonsillectomy was a urinary acidity encountered which approached a point indicative of acidosis. The pH. lay within normal limits in every case.

4. A simple method of testing the urinary acidity is described. It is felt that this will give more accurate information relative to acidosis than the qualitative tests for acetone bodies in the urine. This is especially the case in view of the great increase of total organic acids in the urine known to occur in an acidosis.

I wish to express my thanks to those members of the staff who allowed me access to patients under their care, and to Dr. G. A. Harrison for his kindly criticism and advice.

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FOUR CASES of IMMUNO-TRANSFUSION with remarks on the Method

BY

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Immuno-transfusion is a comparatively recent extension of treatment by blood transfusion and the following case seems worth recording as an example of recovery from a desperate illness after other methods had apparently failed.

Case I. (vide chart).

A boy of two years, suffering from a left-sided pneumococcal empyema, was admitted on September 27th, 1924, to Dr. Thursfield's Ward in the Hospital for Sick Children, Great Ormond Street. Two months previously he had developed whooping cough which was followed by broncho-pneumonia, and he became suddenly worse on the day before admission.

Rib resection with drainage was performed on October 15th, but the child's temperature and pulse remained high, and his condition was still critical. Two weeks later the left testis became tender and swollen; this was thought to be a metastatic infection and confirmation was obtained on November 5th when pneumococci were grown from his blood. The urine was normal. A course of vaccine and serum treatment was tried but failed, and on November 13th, immuno-transfusion was carried out by the method recommended by Colebrook and Storer.[1] A pneumococcal vaccine was prepared from the patient's blood culture and a dose of 1,000 million was injected into his father; five hours later 350 ccs. of the father's blood were removed, defibrinated and injected into the child's median basilic vein. His temperature and pulse fell immediately and by the next morning he was much better.

Except for a rise of temperature on the third day, when he developed a fresh orchitis on the same side, the improvement was maintained for a week, and on November 21st his blood culture was sterile. On November 24th there was a further pulmonary involvement on the opposite side and a small accumulation of pneumococcal pus in the corresponding pleural cavity was removed by aspiration. On this occasion the child's own defences proved adequate to overcome the infection; his temperature and pulse were normal in five days and he was well enough to be discharged from hospital on December 12th, 1924. Since that time he has been well and was seen six months later (June, 1925) when the left lung had expanded, the wound was still healed and his general condition, except for a little residual bronchitis, remained excellent.

It will be seen from the chart that the prolonged administration of polyvalent pneumococcal serum and stock sensitized vaccine, as well as two doses of autogenous vaccine (November 11th and 12th) were without appreciable effect and that the improvement dates from the immuno-transfusion given on November 13th.

It is difficult to be certain what were the principal factors in the child's recovery. Some, no doubt, will attribute it to the vaccine, serum or fixation abscess, but it is our own definite impression that immuno-transfusion was the turning point in the illness, and we think that this is substantiated by the chart.

One of us has treated three other cases by this method and all three have died. Nevertheless septicæmia is such a fatal condition that one success is not entirely discounted by three failures. Brief details of the three latter are given below.

Case II.

A girl of seven years suffering from pericarditis, and with staphylococcus aureus in the blood following an osteomyelitis of the upper third of the femur. One immuno-transfusion was given.

Case III.

A boy of eight years with a very similar bone infection and streptococci in the blood. He had been treated with antistreptococcal serum and two doses of perchloride of mercury (one-thirty-second and one-fortieth of grain) intravenously before immuno-transfusion was carried out.

Case IV.

A boy of two years with a streptococcal blood infection following a post-auricular abscess. Disease of both middle ears and thrombosis in one lateral sinus were demonstrated post-mortem. This child was given two immuno-transfusions.

It is noteworthy that recovery occurred in the pneumococcal infection, and such cases do not appear to have been treated by this method.

The Origin, Progress, and Criticisms of the Method.

Septicæmia has been frequently treated by simple blood transfusion, but the results have been disappointing: Sir Almroth Wright[2] suggests that it may do actual harm by providing additional and better culture medium. The next step[3] [4] was the injection of blood from patients who had recently recovered from the same infection (*e.g.*, typhoid fever and pneumonia) and whose blood was presumed to have a specific power against one particular organism. The artificial production of this immunity in the donor was attempted by Hooker[5] [6] in 1913. Wright[7] elaborated the method and carried out a long series of laboratory experiments. The main bacteriological evidence and clinical results of this work are given in two papers by Colebrook and Storer[1] in the *Lancet* for 1923. The method briefly stated is as follows:—

The donor's blood is tested against that of the patient, and a dose of one thousand million stock staphylococcal or one hundred million typhoid vaccine is injected subcutaneously into the donor. Four to five hours later 500 ccs. of blood (for an adult patient) is removed from the donor, defibrinated and injected into the patient intravenously. The technique of this simple operation is clearly described by Colebrook and Storer (*loc. cit.*). It is important to observe the stated dose and time in order to avoid the possibility of transfusing the blood during the negative phase.

In advancing septicæmias the bactericidal reaction of the patient's blood has been overwhelmed. The mass immunisation response, previously induced in a healthy donor, is transferred to the patient by the immune blood, and reinforces his hæmo-bactericidal power. Furthermore, the addition of many fresh red and white cells must be beneficial.

Much has been written on the relative advantages of using whole and citrated blood in transfusions. Although unmodified whole blood is the ideal, its use has been restricted by technical difficulties. Citrated blood is free from these, but is unsatisfactory inasmuch as the red blood cells are made more fragile, and severe reactions are produced in from 40 to 50% of cases according to some observers.[10] [11] In addition, it has been shown[12] that the bactericidal efficiency of the blood for staphylococcus and streptococcus is diminished by decalcifying agents. Defibrination overcomes all these difficulties and only entails a loss of 25 to 30% of the white blood cells.

The optimum time for removing the blood after injecting the vaccine has been experimentally worked out by Wright and his colleagues,[7] who find that the maximum bactericidal response is produced in from four to six hours. Wright[2] recommends suitable stock rather than autogenous vaccine for the donor. Undoubtedly there is a non-specific factor in the reaction. In the four cases described, however, autogenous vaccine was used. It is difficult to foretell which cases will respond to immuno-transfusion, but an unevacuated nidus of infection precludes any hope of success from the method. Passive immunity is no weapon against an undrained abscess.

Summary and Conclusion.

1. Four cases of proved septicæmia treated by immuno-transfusion with one recovery and three deaths are described.

2. The success occurred in a pneumococcal septicæmia consequent upon empyema and seems attributable to the transfusion.

3. All four cases had previously undergone surgical operations.

4. Immuno-transfusion, though by no means a certain cure for septicæmia, offers a hopeful line of treatment in some cases.

We are indebted to Dr. J. H. Thursfield, Mr. G. E. Waugh, Mr. H. A. T. Fairbank and Mr. O. L. Addison for permission to refer to their cases, and desire to thank Dr. Thursfield in addition for his help and criticism in the preparation of this paper.

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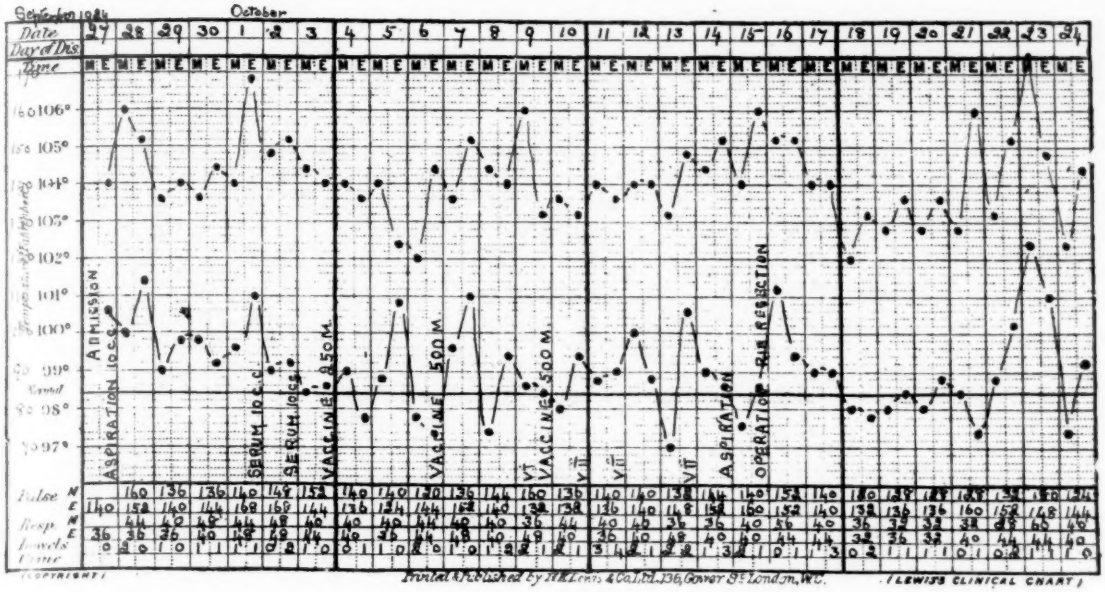
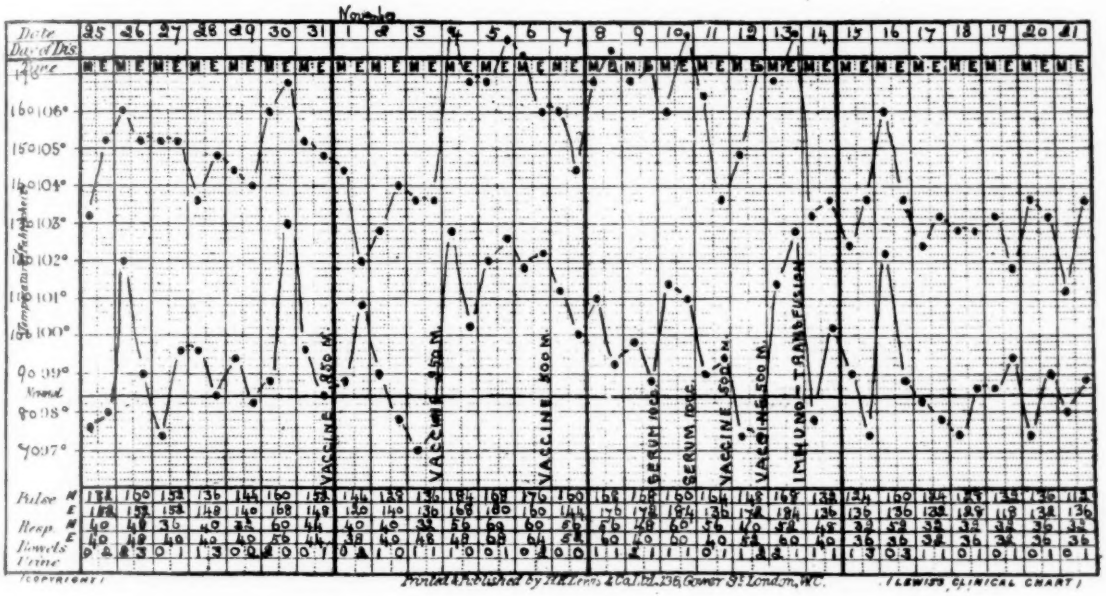
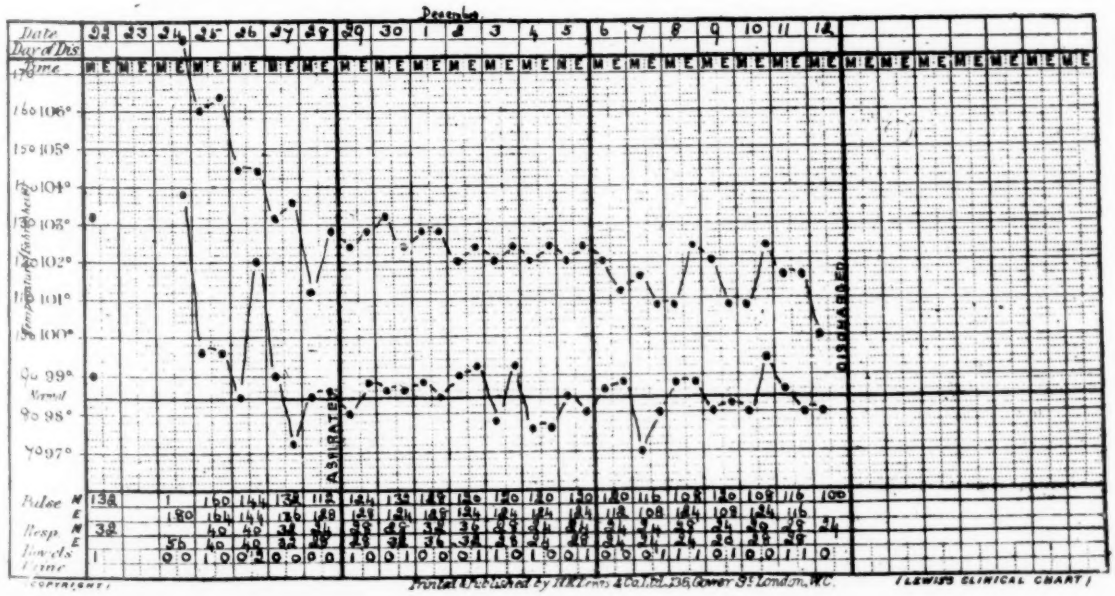
CHART OF CASE I.

(Lower line temperature, upper line pulse.)







NOTES.

1. Polyvalent antistreptococcal serum (Burroughes and Wellcome) was used.
2. The vaccine was stock "sensitized" pneumococcal except that given on Nov. 11th and 12th, which was autogenous.
3. Immuno-transfusion was carried out on Nov. 13th.
4. Patient was discharged on Nov. 22nd and re-admitted on Nov. 24th.

NOTES ON MEASURES IN INFANT FEEDING.

BY

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WITH

HUGH THURSFIELD, D.M., F.R.C.P.

The following notes are written in the hope of once more drawing attention to the danger of using a teaspoon for measuring dried milks.

Some physicians prescribe so many "level teaspoonsful," others so many "heaped teaspoonsful" of dried milk.

Table 1 shows the actual weights of one particular milk as measured out by a series of nurses. The same spoon and the same dried milk were used throughout.

TABLE 1.

Measured by Nurse No.	Weight in gm. of 1 "level" teaspoonful.	Weight in gm. of 1 "heaped" teaspoonful.
1	1·7	2·9
2	1·5	2·5
3	2·1	3·8
4	2·0	4·9
5	2·7	5·0
6	2·5	3·5
7	—	2·5
Highest	2·7	5·0
Lowest	1·5	2·5
Mean	2·1	3·6

It is easy to understand why nurse No. 5 should acquire a reputation for making her babies gain weight, if, say, she took over the duties of nurse No. 2.

That variations do occur owing to the different sizes of different teaspoons is, of course, well recognised, and needs only to be mentioned. In practice one particular spoon is usually put aside for the purpose of measuring the food, or, as in institutional work, it may often happen that all the teaspoons are of the same pattern.

That one milk powder is lighter than another is frequently obvious to the naked eye, but we feel that the extent of the variations due to the different densities of different foods is not properly appreciated. In Table 2 are included a number of the foods commonly used in infant feeding.

TABLE 2.

Showing the variations due to the different densities of different foods. All the measurements were made by the same person with the same teaspoon or tablespoon.

Substance weighed.	Weight in gm. of 1 level teaspoonful.	Weight in gm. of 1 level tablespoonful.
A	1·0	5·8
B	1·5	7·0
C	1·5	7·4
D	1·9	8·6
E	1·9	9·0
F	2·0	8·5
G	2·0	9·1
H	2·0	8·3
I	2·3	10·0
J	2·4	12·5
K	2·9	14·5
L	3·0	14·3
Casein	2·3	10·0
Dextri-maltose	2·9	14·8
Cane-sugar (granulated)	4·3	21·9

The difference in density alone might easily account for an improvement on changing the diet from one food to another.

The practical importance of these facts may be illustrated by the following examples. A certain well-known dried milk (which we will call D) has the following composition :—

	Grammes of		
	Carbohydrate.	Protein.	Fat.
100 gm. of the dry milk powder contain	41·0	22·2	27·4

On reconstituting milk from this powder by the addition of water, according to the instructions on the tin, it is generally believed that the resulting mixture will have approximately the same composition as cow's milk. From the instructions it is learnt that the mixture is to be made in the proportion of 1 teaspoonful of powder to 2 tablespoonsful of water. Let us assume for the moment that the powder measured in 1 teaspoon *weighs* 1 drachm or 3·55 gm. and that the volume of 2 tablespoonsful of water is 1 ounce or 28·4 cc. In other words let us suppose that we are prescribing "one drachm to the ounce." One drachm to one ounce, or 3·55 gm. to 28·4 cc. is the same as 12·5 gm. to 100 cc. Knowing the composition of 100 gm. of milk powder D it is easy to calculate the composition of 12·5 gm.

	Grammes of Carbohydrate.	Protein.	Fat.
12·5 gm. of milk powder A contain ...	5·1	2·8	3·4

And of course our mixture of 12·5 gm. powder D and 100 cc. water will contain the same. The composition of cow's milk varies, but the following is a fair average :—

	Grammes of Carbohydrate.	Protein.	Fat.
100 cc. cow's milk contain	4·5	3·0	4·0

It will be seen therefore that the belief that reconstituted milk has approximately the same composition as fresh cow's milk is correct, *on the above assumption*—but what an assumption it is ! One level teaspoonful of powder D according to our measurements, weighs only 1·9 gm ! Let us suppose that the ounce of water is measured out in a measure (and this is a common practice) and correctly. Then 1·9 gm. to 28·4 cc. is the same as 6·7 gm. to 100 cc., and

	Grammes of Carbohydrate.	Protein.	Fat.
6·7 gm. powder D contain	2·7	1·5	1·8

The concentration of this mixture is approximately half that which both manufacturer and physician imagine the infant is receiving

In order to give the reader an opportunity of checking our findings in Table 2 we would mention that the teaspoon we used held 4½ cc. of water and the tablespoon 22½ cc. This brings us to another point—the size of the tablespoon. The tablespoon employed was the standard pattern commonly used in the wards at the Hospital for Sick Children and did not strike us as unusually large. It was rather astonishing to find that its cubic capacity was nearer one ounce than half an ounce.

There is one other point. It is not unknown for a physician to claim that his infant patient has so many calories per diem, knowing that his nurse measures the dried milk he orders with a teaspoon. Suppose he prescribes milk powder D, seven feeds in the 24 hours, and each feed ʒiii ad ʒiii. He makes his calculation of the intake of calories on the basis that ʒi corresponds to 3·55 gm. of milk powder D :—

$$21 \times 3{\cdot}55 = 74{\cdot}55 \text{ gm. in 24 hours.}$$

100 gm. contain 41·0 gm. carbohydrate, 22·2 gm. protein, and 27·4 gm. fat, which yields 514 calories ([41·0 + 22·2] × 4·1 plus 27·4 × 9·3). Therefore 74·55 gm. milk powder D yield 383 calories.

He calculates that his patient is receiving 383 calories in the 24 hours. According to our measurements, however, the patient only receives 21 × 1·9 or 39·9 gm. of milk powder D which yields 205 calories, or just over half what he is supposed to be having.

The remedy for all this is, of course, obvious. If the physician really wishes to know how much is being given to his patient, or if he wishes to calculate the caloric intake, he must have the dried milk weighed. We do not wish, of course, to suggest that it is necessary for every infant to have every particle of food weighed. Children were fed before balances were invented. Mothers and doctors have learnt from experience the quantities required, whether they employ teaspoons as a rough measure, or whether they judge the amount by eye. But real knowledge can only be acquired on the basis of accurate quantitative data, and teaspoonsful do not make for accuracy.

There is just one other practical point. It would be convenient if the manufacturer's directions did lead to a reconstitution of milk of approximately the same composition as cow's milk or human milk. We have shown that the present method does not do so. Setting aside the use of the balance which is not practical politics for the majority, can anything else be done? Some firms supply a special measure with each tin of infants' dried food. These measures are open to the same objections as the teaspoon (Table 3) with this difference—that the measure could easily be made of such a size as to contain *on the average* 3·55 gm. of the particular dried food. This would in the long run be an improvement on the teaspoon.

TABLE 3.

Showing the variations using the measure supplied by the trade with the tin of infants' dried food K.

Measured by Nurse No.	Weight in gm. of 1 measureful.
1	5·0
2	4·0
3	5·0
4	4·9
5	4·6
6	5·0
7	4·6
Highest	5·0
Lowest	4·0
Mean	4·7

Table 3 shows the results of our experiments using one such measure supplied with dried food K. It will be seen that in our hands this measure was too large (mean measureful 4·7 gm.), but it will be noted that the variations between the results given by different nurses was much smaller than in the case of the teaspoon. The firm supplying this measure, to our mind, quite spoiled a step in the right direction by giving instructions on the label of the tin to use so many measurefuls *or teaspoonsful*, thus suggesting, perhaps unintentionally, that the measure and a teaspoon were of the same capacity! Our teaspoonful of this particular food weighed 2·9 gm. As an alternative for the manufacturer we would suggest that he might do

what we have done, viz., determine the weight of his food contained in an *average* level teaspoonful. It would be helpful if he would state what was the capacity of the teaspoon he regarded as of *average* size, in the same way that we have stated that our teaspoon held $4\frac{1}{2}$ cc. of water; or better still, perhaps the manufacturers would consider jointly the possibility of adopting and supplying some standard measure. Having fixed the measure it would only be necessary to alter the instructions on the tin so that when X measurefuls were added to Y ounces of water the resulting reconstituted milk approximated in composition to that of cow's milk, or of human milk whichever be taken as standard. It would be a matter of relatively simple experiment to determine X and Y, and to arrange that they were convenient whole numbers.

An Investigation of SCLEREMA NEONATORUM; with Special Reference to the Chemistry of the Subcutaneous Tissues.

(Part I.)

BY

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WITH

A HISTOLOGICAL REPORT

BY

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Introduction.

Sclerema neonatorum is a rare but interesting condition peculiar to infants. The extraordinary confusion that has existed in the past in regard to nomenclature will not be discussed. Instead the reader is referred to an article by Langmead[9]. The five cases reported in this paper would probably be diagnosed as "pseudo-sclerema," using the term in the sense employed in Langmead's article. I personally would prefer to follow Paterson[27] in regarding them as examples of the milder type of true sclerema.

Dr. J. W. McNee first became interested in the disease in 1921[20] when the first of the five cases was seen in consultation with Mr. C. C. Choyce and Dr. A. M. H. Gray. With Dr. Gray a preliminary communication was made at the Dermatological Section of the Royal Society of Medicine, but publication was postponed in the hope of obtaining further material for fuller chemical examination. In 1924 this opportunity arose. In the meanwhile I had learned of my colleagues' previous observations, and am greatly indebted to them for permission to include their findings in Cases I. and II. In this work I have also been aided by numerous other colleagues to all of whom I desire to express my thanks. I would mention particularly Mr. H. J. Channon, of University College, who was responsible for many of the analyses in Cases III. and IV. and controls No. (a) and (d).* I wish to

* Mr. Channon has already published with the author an extract of the purely chemical findings in the *Biochemical Journal*, 1926.

thank Mr. R. J. Bromfield and Mr. D. S. Martin for their invaluable assistance. The Medical Research Council very kindly made a grant towards the expenses of the original drawings.

First will be given the clinical findings in the five cases, with post-mortem reports in four. The fifth case recovered. Then in order the following investigations will be reported, viz., histological examination of the subcutaneous tissues, histochemical examination of crystals in subcutaneous fat, X-ray examination of the subcutaneous tissue and related chemical findings, examination of the cyst fluid from Case III., and chemical investigation of subcutaneous tissues.

Clinical Findings.

A brief outline only of the clinical findings in the five cases will be given, since there is nothing to add to previous accounts. The reader will find a very full description with a bibliography exceeding 200 references to the literature up to 1895, in Ballantyne's work[2]. A more recent treatise to which reference should also be made is that of Paterson[27]. Other papers of interest are those of Garrod[10 & 11], Northrup[25], Sobel[33], Scott[30], and M'Neil[21]. Other references will be found later in the different sections of this paper.

Case I.

L.W.H., male, aged six weeks, a first child, was admitted to University College Hospital, under Mr. C. C. Choyce, on January 23rd, 1921. The labour was normal, and nothing peculiar was observed in connection with the baby until the second day after birth, when a lump appeared on the left arm. This was thought to be an abscess, but was not at first opened. Lumps then appeared on other parts of the limbs and body. Subsequently an incision was made into the lump over the left deltoid muscle and a milky fluid escaped, but nothing resembling pus. The child was emaciated and pallid. He had never been breast fed. Irregular hard well-defined thickenings of the subcutaneous tissue were present over both upper arms, over the upper part of the back and the nape of the neck, and smaller areas of thickening over both thighs. The skin was firmly adherent to these swellings and was of a deep purplish colour, especially in the region of the left deltoid, where the swelling had undergone softening. The colour of the skin on the thighs was less purple. The milky fluid could be squeezed out in abundance from the incision into the lump over the deltoid muscle. This fluid, under the microscope, was found to contain myriads of acicular crystals, along with a certain number of cells of lymphocytic type. The fluid was examined under crossed Nicol's prisms, but the crystals were not observed to be doubly refracting to light. In considering subsequent observations this examination was probably wrong. Cultures of the fluid on all ordinary

culture media remained sterile. Films examined for spirochætes by dark-ground illumination, and stained by Fontana's method, were all negative.

A Wassermann reaction on the mother's blood, carried out on January 24th, was completely negative. The child's blood is said to have been similarly examined previous to admission with negative result.

The child's weight on admission was 7 lbs. 8 ozs. On February 2nd, nine days after admission, it was 7 lbs. 10 ozs. Some days after admission the swelling in the deltoid region in relation to the incision became much enlarged, and definitely fluctuant. It was not reddened, however, and was not dealt with surgically. The temperature during the period of residence was much more often subnormal than normal, and was often lower at night time than during the morning. On several occasions, however, fever was present, although never for longer than 24 hours at a time, the temperature on three occasions being 99·2°, 101°, and 100·2°.

On February 3rd a wedge was removed from the swelling on the upper arm for diagnostic purposes.

The infant made no progress and died on February 9th, 16 days after admission.

Post-mortem report (Dr. J. W. McNee).

Child emaciated and pallid. Localised swellings in the subcutaneous tissues of the upper arms, back, and back of neck were still readily palpable in the cadaver. A fluctuant swelling over the left deltoid muscle was incised, and fully half an ordinary test-tube full of milky fluid esaped. This fluid was obviously not pus. On cutting into various parts of the subcutaneous tissues of the body the following points were made out. The subcutaneous fatty tissue was in most places reduced to a very thin layer. In other areas, corresponding to the palpable swellings, the subcutaneous fat was locally increased in amount, and macroscopically showed various differences from the normal. It was of a chalky white colour, without a trace of yellow, and the fibrous trabeculæ were very sharply defined so as to give the tissue an appearance almost approaching that of the pancreas or a salivary gland. It was firm to touch, and had a peculiar lard-like consistency.

The heart and lungs were normal. The stomach was much dilated and the pylorus was distinctly hypertrophied to form a mass about the size of a broad-bean. Liver, kidneys, spleen, and intestinal tract normal. The adrenal glands were small, and their cortex appeared to be devoid of lipoid fat. The testicles were undescended and lay in the inguinal canal.

Portions of skin and subcutaneous tissue were removed for histological and chemical investigation (*see* later).

Case II. was under the care of Dr. R. Hutchison at the Hospital for Sick Children, Great Ormond Street.

P. A. D., female, aged 12 weeks, admitted September 22nd, 1921, with a three days' history of diarrhœa, but no vomiting. The baby was born at full term, the labour being normal. She was the second child, her brother being alive and well. The mother was healthy and had had no miscarriages. The baby was breast fed for a month and was then given Nestlé's milk and lime water. On examination there was marked dehydration, and a slight enlargement of the liver, but otherwise nothing abnormal. The temperature fluctuated between 98° and 103° F. Death occurred September 29th from ileo-colitis.

Two days before death the subcutaneous tissues became hard and board-like. (Body temperature 103° F.) On the next day the sclerematous deposits were more marked. There was no pitting on pressure.

Some authorities would probably place this case in a separate category from the other four on account of the clinical history. It has been included because the histological examination showed the same picture, though less marked, as in the other cases.

Post-mortem report (Dr. Donald Paterson).

The body was that of a fairly well nourished child, but the subcutaneous tissues were hard and firm due to the condition of sclerema. The weight was 8 lbs. 10 ozs. and the length 23 inches. Both small and large intestines had a flannel appearance throughout. Petechial hæmorrhages were present, and the colon was definitely thickened. No ulcers were seen. The mesenteric glands were much enlarged. The liver had a fatty appearance. The kidneys exhibited cloudy swelling and fatty degeneration, and uric acid infarcts were noted. Skin and subcutaneous tissue was removed from the buttocks and the abdominal wall for histological and chemical examination by Dr. McNee.

Dr. D. Nabarro isolated B. dysenteriæ (Flexner Y) from a scraping from the colon.

Case III. was under the care of Dr. Hugh Thursfield at the Hospital for Sick Children.

L. H.,* female, aged 5 months, admitted April 3rd, 1924. The baby was born at full term, the labour being normal. Red patches "hard and raised" were noted on the skin of the arms on the first and second days of life. On the fifth day the arms and legs were "stiff." Later on, lumps appeared under the skin of the arms and legs. The weight at birth was 8½ lbs., and on admission 10¼ lbs. The baby was bottle-fed from birth. It was given No. 1 Virol on the first day of life, and until admission it was fed

* This case was shown for Dr. Thursfield at the Royal Society of Medicine(37).

on a mixture of Virol and cow's milk in the day time, and cow's milk and whisky (10 drops to a feed) at night. The patient was the youngest of a family of eleven, of whom nine were healthy and one died of marasmus.

FIG I.

On examination the child appeared well nourished and normal in every way except for the subcutaneous tissues. Therein could be felt firm hard patches which were adherent to the skin and which did not pit on pressure. These were present in both arms, both forearms, both buttocks, the extensor surfaces of both thighs, both calves, and on the back. There was a small fluid cyst over each deltoid muscle (*see* Figure 1). One of these was aspirated and the contents examined chemically (*see* later). The Wassermann reaction was negative. The fæces were normal macroscopically and microscopically. Nothing abnormal was found in the urine.

On April 17th, 1924, a biopsy was performed by Mr. E. I. Lloyd, who removed a portion of the skin and subcutaneous fat from the right forearm. The wound healed by first intention. The histological and chemical examinations of the excised tissue are reported later.

Shortly after the operation the infant developed gastroenteritis from which it died on May 5th, 1924. The weight remained stationary from admission till the biopsy. Thereafter it fell rapidly from 10 lbs. 7 ozs. to 8 lbs. 6 ozs. During this period of decline, the subcutaneous lumps softened and became absorbed to a considerable extent. The temperature from admission until the operation was 97° F.—100° F., though it exceeded 99° on only a few occasions. After the operation until death it varied between 98° and 102°.

Six days after the biopsy the blood was examined; the blood-sugar was 67 mgm. per 100 c.c. half an hour after a feed, and the serum cholesterol was

only 59 mgm. per 100 c.c., whereas the blood of a control baby, 5 weeks old, contained 143 mgm. There was no lipæmia.

Post-mortem report (Dr. W. G. Wyllie).

The body was greatly emaciated: weight 7 lbs.; length, 2 ft. 2 in. A small cystic swelling, the size of a marble, was present under the skin of each arm, over the deltoid muscle. Under the skin of the forearms and of both legs were many small firm lumps. The skin over the buttocks was thick and brawny to the touch. Portions of subcutaneous fat were removed for chemical and histological examination (*see* later) from the buttocks and back of the thighs and arms. Throughout the fat thus removed were scattered minute cysts similar to those over the deltoids. Each cyst was full of a white, shiny, soft glistening material like "snow cream," which had a strong smell of lanoline and camphor. The subcutaneous fat elsewhere was dry and firm. The viscera in the thorax and abdomen (apart from the intestines), and the brain, revealed no abnormalities. Microscopical examination of sections of the pituitary, thymus, thyroid, pancreas and suprarenals, revealed nothing of note.

Case IV. was under the care of Dr. H. C. Cameron at Guy's Hospital.

S. E. B., male, aged 4 days, admitted April 3rd, 1924. The baby was born with blue asphyxia, the labour being normal. When 24 hours old cyanosis recurred, but there was no distress. Subsequently there were several similar but slighter attacks of cyanosis. There was diarrhœa with green stools, but no vomiting.

The scleremátous deposits were similar to those described in Case III. but were more extensive: both cheeks were involved. The baby took well from the bottle. The temperature fluctuated slightly on either side of 98° F., but was never definitely subnormal. On two or three occasions it rose to 101° and 103°. The weight on admission was 2,800 grammes, and had risen slowly to 3,000 grammes when discharged from hospital on May 7th, 1924. The following estimations were made on the blood: cholesterol in whole blood 183 mgm., in plasma 120 mgm. per 100 c.c. (Prof. A. Stokes): sugar in whole blood 61 mgm., inorganic phosphates in serum 5 mgm., serum calcium 9·3 mgm. per 100 c.c. (Dr. W. W. Payne). The plasma and serum were both definitely lipæmic. A blood count resulted as follows: hæmoglobin 74 per cent.: erythrocytes 3,960,000: leucocytes 10,200 of which the polymorphs constituted 64·25, lymphocytes 32·25, large mononuclear cells 1·75, eosinophils 1·5, and transitional cells 0·25 per cent.

The infant was readmitted on July 2nd with infective enteritis, from which it died the next day.

The post-mortem examination (Prof. A. Stokes) revealed nothing of note apart from the condition of the intestines and the subcutaneous fat; some of the latter was excised for histological and chemical examination (*see* later).

Case V. was under the care of Dr. Hugh Thursfield at the Hospital for Sick Children.

E. H., female, aged 6 weeks, admitted November 11th, 1924. The baby was brought to hospital on account of " fits " and " blue turns " which started in the first week of life. She was born at full term, the labour being normal. She is the third child, the other two being alive and well. The mother is healthy and has had no miscarriages. Weight at birth 7 lbs. and on admission 7 lbs. and rose gradually to 7 lbs. 8 ozs. on December 12th. Temperature fluctuated between 97° and 99° F. The liver and spleen were both enlarged slightly, otherwise the various systems appeared normal. The condition of the subcutaneous tissues was similar to that in the other cases, but much less marked in degree. There was no cyst formation and no deposits in the cheeks. The mother noticed that the buttocks were hard in the first week of life. The Wassermann reaction was negative. Nothing abnormal was found in the urine. On November 11th the blood was examined: serum calcium, 15 mgm., plasma inorganic phosphate 4·8 mgm., and plasma cholesterol 140 mgm. per 100 c.c.

The infant slowly gained weight and improved generally, the sclerematous deposits slowly absorbing till recovery became complete in the sixth month (*see* later in section on X-ray examination). On February 5th, 1925, a second examination of the blood was made: serum calcium 11·8 mgm., serum cholesterol 178 mgm. per 100 c.c.

At the age of 10 months the infant still had fits though these were less severe and less frequent. It was very doubtful whether the child had ever been able to see. Both the mother and the ward-sister considered she was blind. Nothing abnormal was found on examining the fundi and optic discs. An X-ray of the skull showed no abnormality.

Histological Examination of the Subcutaneous Tissues.

(J. W. McNee.)

Case I.

(Biopsy and Autopsy Material.)

A few days before death, a small wedge-shaped piece of skin and subcutaneous tissue had been removed, for histological examination, from a large firm swelling over the right deltoid muscle. At the necropsy a number of pieces of skin and subcutaneous tissue were taken from different situations, so as to include specimens looking very different to the naked eye. The tissue comprised some of the obvious swellings, other areas where the skin was only slightly raised above the neighbouring parts, and also segments of what appeared to be the normal skin and subcutaneous tissues of the infant.

Some of the tissue was fixed at once in 10 per cent. formalin, while the remainder was put aside for chemical analysis. Sections of the material fixed in formalin were cut both by the freezing microtome and after paraffin embedding. The frozen sections were stained in various ways, chiefly with Hæmalum and Sudan III, and with Lorrain Smith's Nile Blue Sulphate. The paraffin sections were stained in the usual way with Hæmalum and Eosin.

The histological changes are described below, and are most striking in the subcutaneous tissue from the obvious swellings. The lesion is the same, but less fully developed, in places where the skin is only slightly raised above the general body surface. In the parts noted macroscopically as normal, the pathological changes are still found microscopically, but are minimal in amount. It may be said at once that the true skin is normal histologically, the lesion being strictly confined to the subcutaneous tissues.

In sections of tissue from one of the obvious swellings, the first thing noted, both in frozen and paraffin sections, is the very great increase in thickness of the fibrous trabeculæ which separate the lobules of fat. This was also noticed macroscopically.

A separate description is necessary for the frozen and paraffin sections, since the two methods specially favour the examination of different histological details.

In a paraffin section, from which all fat has of course been removed, the structure of the fibrous trabeculæ is seen to be much altered from the normal. The fibrous tissue is increased in amount, and in many situations is broadened out into irregular patches, some containing fat spaces in small numbers embedded in them, others entirely devoid of fat cells. Throughout the tissue, and more especially in relation to the empty circles representing fat cells, are numerous irregularly distributed thin clefts, indicative of the presence of crystals dissolved out in the paraffin process. With higher magnification these clefts are seen completely to surround every fat cell, and in a few places where a fat cell has been cut in tangential section near its surface the clefts are found crossing the cell in all directions. It is evident that they entirely surround the cells like the cover of a ball. Similar clefts are also numerous in the fibrous tissue quite away from any recognisable fat cells. Lying in contact with many of the clefts are elongated giant cells, with large multiple nuclei. Another histological change is noted in parts of the tissue where fat cells have lain close together, separated by only a small amount of connective tissue. This is the deposition of lime salts, recognised by their density, shape, and deep purple staining reaction with hæmalum. These salts of lime are seen to form a coating to the fat cells, and where they occur the clefts are absent. Throughout the fibrous tissue generally, considerable infiltration with round cells is seen.

In frozen sections, the finer structure of the fibrous tissue is less obvious, but the fat cells and the undissolved crystals can be more carefully examined.

The appearances are well shown in the coloured plate (Fig. 2). The crystals are seen in enormous numbers, acicular in shape, and lying in bunches like sheaves of corn. They are greyish in colour under the microscope, and are quite unstained either by Sudan III or by Nile Blue Sulphate. The fact that the fat cells (containing neutral fat) are surrounded by these crystals, inferred from the paraffin sections, is entirely confirmed. The fat cells themselves take up the Sudan III and Nile Blue stains quite well, but show various differences from the normal colour by these methods. The colour is not so bright as usual, but flecked and mottled with grey. It is impossible to make out definitely, even in the thinnest frozen sections, whether this alteration in colour is due to crystals shining through from behind, or to an actual abnormality in the fat content of the cells. On examining the frozen sections through crossed Nicol's prisms, all the crystals are found to be doubly refracting to light. The fat cells themselves show numerous points of double refraction to light, but the appearance is not uniform. It is impossible to be sure if the appearance is due to material contained within the cellular protoplasm, or to fragments of crystals lying behind or on top of the cells.

Case II.

(Autopsy Material.)

Histologically, a very mild degree of the changes seen in Case I. is recognised. In paraffin sections there is an increased thickness of the fibrous trabeculæ, which are here and there widened out into nodes of cellular tissue, surrounding some fat cells, and containing only an occasional giant cell. In one portion only, close below the cutis, clefts are seen from which crystals have obviously been dissolved out. The giant cells are most numerous in the area surrounding these clefts. The blood vessels in the sections examined do not show endarteritis, as in other more advanced cases in the series. No calcification of fatty cell envelopes is made out.

Case III.

(Biopsy and Autopsy Material.)

Here the appearances in paraffin sections (Figs. 3 and 4) are closely similar to those in Case I., but giant cells are an even more striking feature while calcification is absent. It happened that sections were cut so as to include an area where the tissue had entirely broken down to leave a space filled with milky fluid (Figs. 3 and 6). The walls of this space are formed by rows of giant cells, which give a very striking histological picture. Endarteritis of small arterioles (Fig. 5) in the subcutaneous tissue is well marked, further evidence of the chronic inflammatory changes which have taken place.

In frozen sections stained by Sudan III and examined under crossed prisms, the changes noted are identical with those of Case I., doubly

refracting acicular crystals being visible almost everywhere. An interesting finding is made out by examination of the wall of the cavity (Fig. 6) which contained milky fluid. Various tags of fatty tissue, containing both neutral fat and crystals, are attached to the wall and project into the cavity. It is obvious that the cavity has been formed simply by death of a small lobule of fatty tissue, and liberation of the neutral fat and crystals from the cells.

Case IV.

(Autopsy Material.)

This is the most striking case histologically of the whole series, owing to the depth of subcutaneous tissue involved. The changes are the same as described for Case I. The formation of firm fibrous trabeculæ, the occurrence of abundant giant cells, of necrosis of fat cells, of calcification, and of inflammatory changes in small arterioles (endarteritis obliterans) are all visible abundantly. In this case too the firm fibrous trabeculæ in the area involved continue as thick strands into the muscular tissue below, but giant cell formation does not extend deeper than the subcutaneous fatty tissue.

In frozen sections, stained for fat, the sheaves of crystals between and surrounding the fat cells are seen in enormous numbers, and through crossed Nicol prisms the picture is brilliant (Fig. 7).

It will be seen from Dr. McNee's report that all four cases showed the same histological picture but in varying degree. The fifth case recovered and no biopsy was made. The histology of sclerema neonatorum has been described previously, for example by Ballantyne[2], Paterson[27], Keilmann[13], and Brinchmann[5]. Keilmann describes his case as "scleroderma." His two illustrations are exactly similar to our paraffin sections.

Histochemical Examination of Crystals in Subcutaneous Fat.

(G. A. Harrison.)

In this section of the paper are recorded attempts to determine the nature of the crystals in the subcutaneous fat.

Observations on Sclerema Crystals.

The appearance of the crystals in stained *frozen sections* as seen under the polarising microscope is illustrated in Fig. 7. They are readily seen under the polarising microscope in unstained sections also, and this fact

Fig. 3.

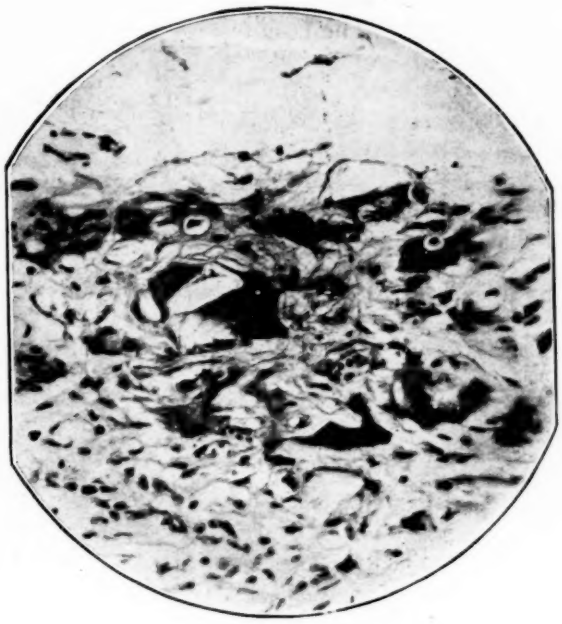

Fig. 4.

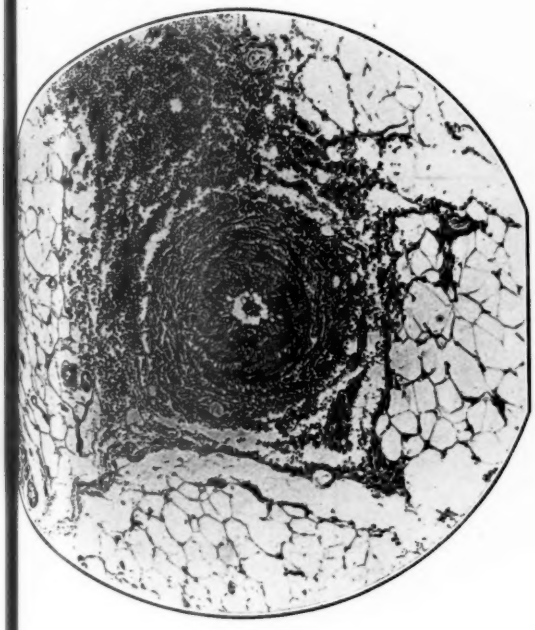

Fig. 5.

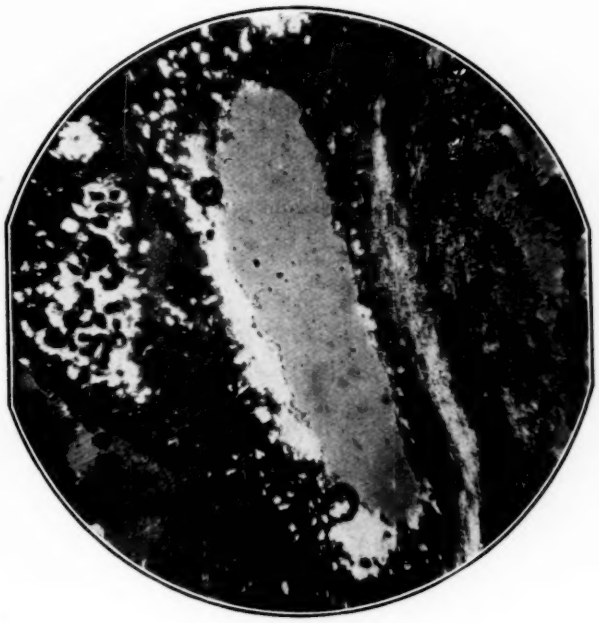

Fig. 6.

made it easy to watch the action of solvents on the crystals. A bunch of crystals was carefully focussed and the section was then flooded with the solvent. The results are summarised in Table I. :—

TABLE I.

Action of solvents on sclerema crystals.

(Frozen sections : polarising microscope.)

SOLVENT.	COLD.	WARM.
Ether.	"Insoluble"	Soluble.
Petroleum ether.	,,	,,
Acetone.	,,	,,
Pyridine.	,,	,,
Alcohol.	,,	Slightly soluble *
Acid Alcohol (1% HC1).	,,	,, ,, *
Alcoholic soda $\frac{N}{10}$.	,,	,, ,, *
Water.	,,	Insoluble. *
HC1. aq $\frac{N}{10}$.	,,	,, *
Na OH. aq $\frac{N}{10}$.	,,	,, *

* Between 40° and 50° C. the crystals melt, to reappear *in situ* on cooling and in the original form.

It is interesting to note that the crystals do not dissolve when treated in this way at "room temperature." It is realised, of course, that the actual temperature of the solvent would in some cases be considerably below room temperature owing to rapid evaporation of the solvent when spread in a thin film on a slide. Table I. shows that the sclerema crystals have the typical solubilities of a neutral fat.

The action of heat on the crystals was similarly studied, the slide being placed on a piece of copper (with central hole) stretched across the stage of the polarising microscope. The copper was then heated. Between 40° and 50° C. the crystals melted and disappeared suddenly. On cooling the crystals suddenly flashed into sight again like so many stars coming out, and

in their original form. There was no suggestion of the formation of liquid crystals. A microscope warm stage for careful measurement of temperature was not available, but the following observations gave a rough measure of the melting point of the crystals in the sections. When placed in an incubator at 37° to 40° C. for half an hour or more, the crystals did not melt, but in a hot-air oven at 50° C. they did. The melting point therefore lay between 40° and 50° C.

Having observed crystals in the frozen sections, the *separated fat* was next examined. A piece of sclerematous subcutaneous fat was warmed on a microscope slide. The melted out fat was covered with a coverslip and allowed to cool to room temperature. As would be expected this separated fat contained anisotropic crystals similar in every respect to those seen in the frozen sections. If the separated fat was cooled quickly the crystals appeared as isolated rods or short needles. If it was cooled slowly, and particularly if it was kept for a few days, the crystals tended to form in tufts of acicular crystals. In their solubilities and melting point, etc., these crystals in the separated fat behaved in every way similarly to the crystals in the frozen sections.

Having observed that the sclerema crystals were soluble in ether, the *ether extract* of sclerematous subcutaneous fat was next examined. A drop of this was mounted under a coverslip, cooled and examined as before. It was found to contain abundant anisotropic crystals, exactly similar in appearance and properties to those found in the frozen sections.

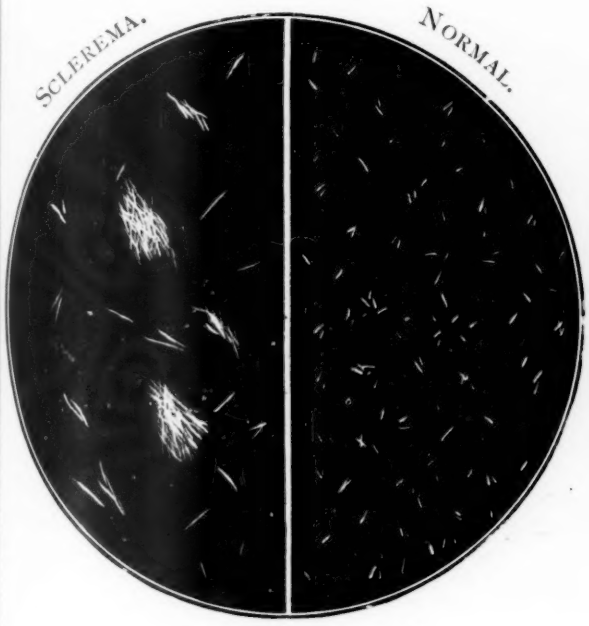

Fig. 9.

Fig. 10.

Similar crystals were found also in the fluid aspirated from a cyst in the subcutaneous fat of Case III. (*see* later).

Observations on "Normal" Crystals.

The next step obviously required was to make control observations. *It was found that the subcutaneous fat of children dying from other diseases, and the subcutaneous fat removed at operation from children requiring surgical treatment, also contained doubly refracting crystals which were very similar in appearance to those seen in sclerema fat.*

The appearance of these crystals as seen in stained frozen sections is illustrated in Fig. 8. Similar crystals were found in the separated fat and in the ether extracts of non-sclerematous children. Fig. 9 illustrates the crystals in frozen sections of sclerematous and non-sclerematous fat ("normal" fat) respectively. Fig. 10 gives a corresponding comparison between the crystals in the ether extracts from the two sources.

The experiments on the solubilities and the effect of warming were repeated on the "normal" crystals, and the results compared with those in sclerema (Tables II. and III.).

TABLE II.

Crystals in Frozen Sections.

SCLEREMA.	NORMAL.
Acicular, in tufts.	Short rods, "bacilli."
Longer than normal.	Shorter than sclerema.
In fat globules and free.	In fat globules only.
Melt at 40°—50° C.	Melt about 30° C.
On cooling reappear quickly above room temperature. Reappear in original form and no liquid crystals.	On cooling reappear more slowly, *e.g.*, in a few minutes at room temperature.
"Insol." in pet. ether at room temperature. Sol. in warm pet. ether.	Dissolve rapidly in pet. ether at room temperature.

In the frozen sections the "normal" crystals melted at a lower temperature than the sclerema crystals. This does not necessarily imply

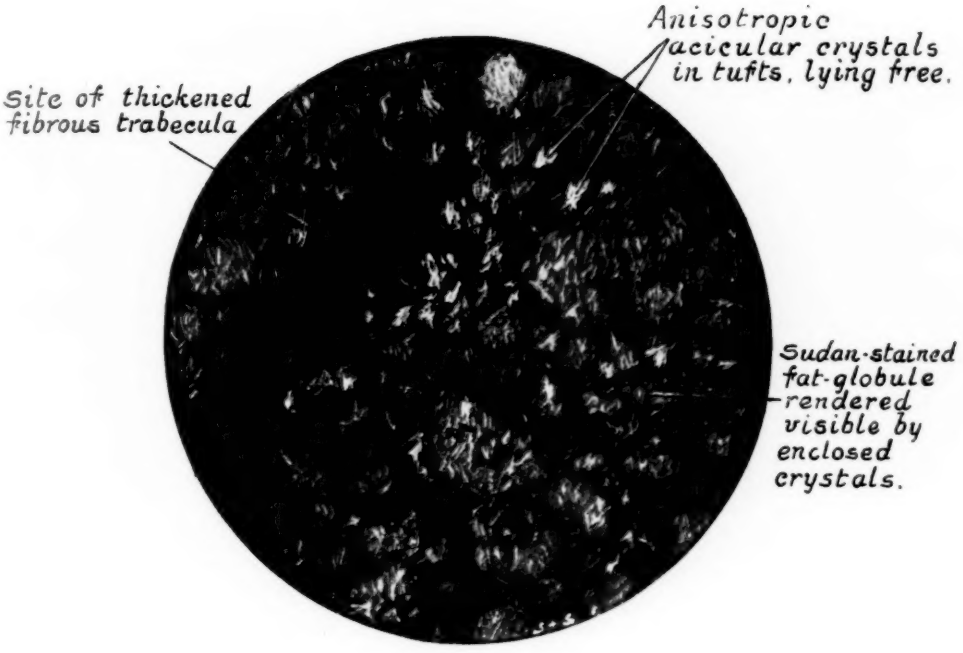
Anisotropic acicular crystals in tufts, lying free.
Site of thickened fibrous trabecula
Sudan-stained fat-globule rendered visible by enclosed crystals.

Fig. 7

Frozen section of subcutaneous fat from case of sclerema. Sudan III. Nicol's crossed. ⅔rds obj. No. 4 eyepiece.

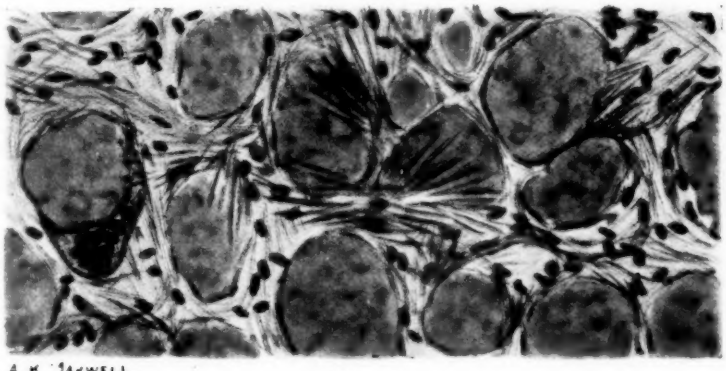

Fig. 2

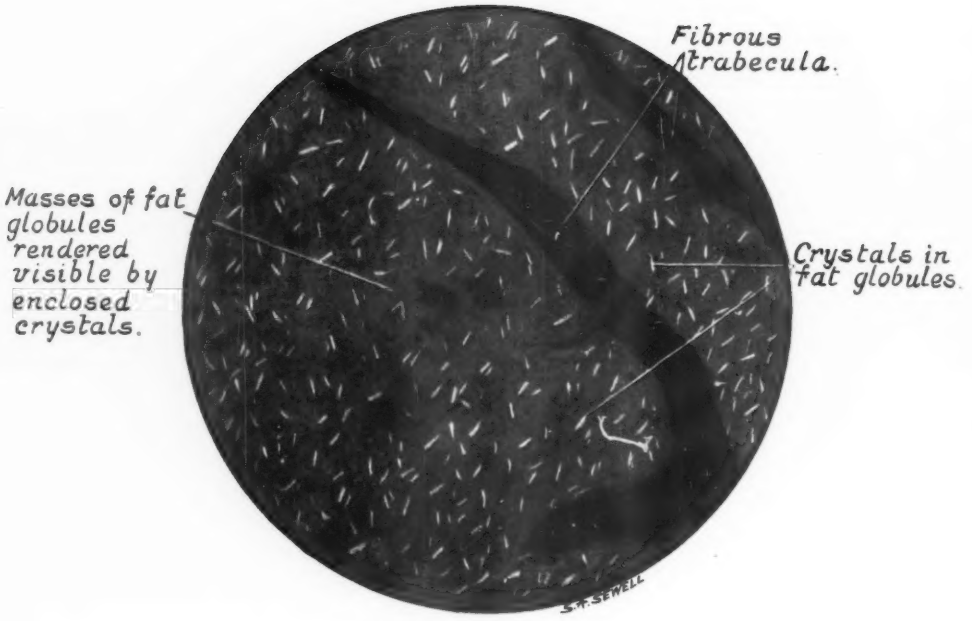

Fig. 8

Frozen section of normal subcutaneous fat
Sudan III. Nicol's crossed. $\frac{2}{3}$rds. obj. No. 4 eyepiece.

that the crystals are different. It might easily result from the media in which the crystals were suspended being of different compositions in the two cases. That this is a possible explanation is seen from Table III.

TABLE III.

	Crystals in Frozen Sections.		Crystals in Separated Fat (melted out under cover-slip).		Crystals in Ether Extract.	
	SCLEREMA.	"NORMAL."	SCLEREMA.	"NORMAL."	SCLEREMA.	"NORMAL."
Crystals melt at	40°-50° C.	about 30° C.	40°-50° C.	about 30° C.	40°-50° C.	40°-50° C.
On cooling, the crystals reappear	quickly and above room temperature	more slowly in a few minutes at room temperature.	quickly and above room temperature	quickly at room temperature.	very quickly and above room temperature, in tufts or as rods.	quickly and above room temperature as rods or in tufts.
Solubility of crystals at room temperature in petroleum ether.	"Insoluble"	Soluble.	"Insoluble"	Soluble.	"Insoluble"	Soluble.

It will be noted that when the "normal crystals" are separated by ether extraction* their melting point rises.

Apart from the slight difference in solubility in petroleum ether (Table III.), the normal crystals behaved towards solvents in exactly the same way as sclerema crystals.

Presumably the "normal" crystals must be either stearin or palmitin, or both. In view of the great similarity between the normal and the sclerema crystals, some observations were made on crystals of pure tripalmitin, and on crystals of pure palmitic acid.

Observations on crystals of pure palmitin.†

Some pure powdered palmitin (M.P. 62°—63·5° C.) was recrystallised slowly from ether at 0° C. Beautiful tufts of acicular crystals were obtained. *These crystals were anisotropic.* This point is emphasised, because most books on histology do not consider the possibility of crystals in frozen sections being palmitin (or stearin). In fact they lead the reader to believe that anisotropic crystals *must* be lipoids. Palmitin and stearin in the liquid state are not doubly refracting, but when crystalline they are. This fact is well known to organic chemists, who in practice frequently employ the polarising microscope merely to see whether a particular organic compound with which they are dealing is crystalline. In other words the property of double refraction is the rule amongst organic compounds when in the crystalline state.

Some of the palmitin crystals were spread on a slide under the polarising microscope. The slide was flooded with ether. At this temperature—the temperature of rapidly evaporating ether—the crystals were not appreciably soluble.

On treating the palmitin crystals with petroleum ether in the same way they did dissolve. In this respect they resembled in behaviour the crystals in the ether extracts from non-sclerematous tissue. In their behaviour to other solvents they resembled exactly the sclerema crystals (*see* Table I.)

Some of the palmitin crystals were heated on the stage of the polarising microscope in the way previously described until they melted to form oily droplets. These droplets were of course isotropic. On cooling, crystals suddenly appeared in each globule as so many stars coming out, providing an exactly similar picture to that seen in the frozen sections and ether extracts of subcutaneous fat.

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* The ether extract of the subcutaneous fat of adults contains similar crystals. Mitchell(22), working on the perirenal fat of an adult, crystallised similar crystals from ether. Under the microscope his crystals somewhat resembled those frequently obtained from flare lards. I have often seen such crystals in the cooled concentrated ethereal solutions of fat obtained by extraction in a Soxhlet apparatus. Frozen sections of the subcutaneous fat of *adults* do not as a rule show neutral fat crystals. Occasionally, however, in sections which have been kept for a long time there is a separation of these crystals.

† I am greatly indebted to Professor J. C. Drummond for the specimens of pure palmitin, and palmitic acid.

Similar experiments with pure palmitic acid.

Experiments similar to those with palmitin were repeated on pure palmitic acid.

Palmitic acid, when crystalline, is anisotropic. Palmitic acid is very much more soluble in ether and in petroleum ether under the above conditions, than either palmitin or the crystals observed in our sections and in the ether extracts from sclerematous and non-sclerematous subcutaneous fat. Moreover of course palmitic acid behaves differently with alcoholic soda. On warming very slightly, palmitic acid crystals mounted in alcoholic soda ($\frac{N}{10}$), are seen to go into solution. On running a few drops of water under the cover-slip an obviously soapy solution results, and crystals are no longer visible under the polarising microscope.

When palmitin or the ether extract from subcutaneous fat (sclerematous or "normal") is similarly treated, the crystals do not go into solution in alcoholic soda (or only to a very slight degree, *see* Table I.). The crystals melt if the temperature is raised sufficiently high. On running a few drops of cold water under the cover-slip, a suspension of fat is obtained but no suggestion of a soapy solution. Moreover, the crystals of the neutral fat are again visible under the polarising microscope, suspended in the water.

Other Tests on Sclerema Crystals.

Microchemical tests for cholesterol in both normal and sclerema frozen sections were negative. The crystals themselves (normal and sclerema) were stained neither by Sudan III nor by Scharlach R nor by Nile Blue Sulphate.

Langer[15] in 1881 referred to the presence of crystals in the subcutaneous fat and discussed the likelihood of their being stearin and palmitin. He noted that the so-called "margarin" crystals seen in the fat of adults had melted by the time the temperature had been raised to 37° C., and considered that they first appeared after death. He stated, however, that a large part of the fat in the fat-cells of infants was solid and opaque at temperatures above body-heat. He declared that this fat did not became fully soft till 40° C.

No doubt most histologists have noted that fat crystals may frequently be seen in frozen sections of subcutaneous fat, but very few references to the fact are made in the literature. In truth it is noteworthy that in discussions on crystals observed in pathological subcutaneous tissue, it is only rarely that the possibility of their being neutral fats is raised. Indeed, a study of the literature of the last 40 years reveals a large number of instances in which acicular crystals have been *assumed* to be fatty acids without there being any chemical evidence whatever as to their nature. Again, anisotropic

acicular crystals have almost invariably been *assumed* to be cholesteryl esters or "cholesterol fatty-acid mixtures"; the possibility of their being neutral fat crystals has scarcely been mooted.

X-Ray Examination* of Subcutaneous Tissue and Related Chemical Findings.

Case III. was X-rayed at the suggestion of Dr. Hugh Thursfield, with the result depicted in Fig. 11. In Case V. the findings were similar. (Fig. 12.) Case IV. was X-rayed at Guy's Hospital with negative result. This may have been due to the use of rays which were too hard, since chemical analysis showed a marked increase of calcium in the subcutaneous tissues. (Table IV.) In a series of non-sclerematous children X-rayed in the same way as the sclerema cases, similar opacities in the subcutaneous fat have never been observed.

Fig. 11 (a).

Fig. 11 (b.)

* I am indebted to Dr. B. Shires for the X-ray examination in Cases III. and V.

Fig. 12.

The results of estimations of calcium and of total phosphorus in the "ether-extracted residue" from Cases III. and IV. are shown in Tables IV. and V. Case V. recovered and no biopsy was performed. No calcium and phosphorus estimations were made in Cases I. and II. These results confirm the presence of the calcification suggested by the histological examination. They provide a likely explanation of the X-ray appearances.

There was no direct evidence as to the form in which calcium existed in the subcutaneous fat, but it was of interest to calculate the ratio of calcium to phosphorus (Table V.). These figures are not contrary to the natural assumption that the calcium was combined as phosphates.

TABLE IV.

Calcium Determinations.

Subcutaneous Tissue.	Case III.		Case IV.	Normal Control.
	Biopsy.	Autopsy.	Autopsy.	
Ca in ether ext.	Nil.	Nil.	Nil.	Nil.
Ca in ether-extracted residue	0·262	2·615	0·254	0·072
Ca as % dry wt.	0·072	1·284	0·065	0·010
Ca as % wet wt.	0·033	0·505	0·030	0·007
Ca in serum— mgm. per 100 c.c.	—	—	9·3	9 to 11

(Case V.: 15 mgm. and later 11·8 mgm. per 100 c.c. serum.)

TABLE V.

Calcium and Phosphorus Estimations.

Sclerema.	Case III.	Case IV.
Phosphorus % (as P.) in ether-extracted residue.	1·41	0·47
Calcium % (as Ca) in ether-extracted residue.	2·62	0·25
The ratio Ca/P in ditto.	1·85/1	0·54/1
The ratio (Ca/P in $Ca_3(PO_4)_2$ is	1·965/1	
P. calc^d. to combine with Ca if as $Ca_3(PO_4)_2$	1·33	0·13
Therefore P. existing in other forms	0·08	0·34

It is of interest to note that in Case V. the X-ray appearance persisted long after the hard masses had disappeared. On November 4th, 1924, the X-ray appearances were typical (cf. Fig. 12). On January 2nd, 1925, it was difficult (by palpation) to detect anything abnormal with the exception of a slight thickening in the subcutaneous fat round the anus, but the X-ray appearances were but little altered. In February, 1925, the calcified patches

were still visible in the radiograms, but appeared less marked. Clinically at this time the subcutaneous fat everywhere was of a normal consistency. In July, 1925, no opacities were visible in the X-ray plates.

Morse[24] has reported a case of calcification of the skin in a child aged 3½ years. He presents radiograms which are very similar in appearance to ours though more marked in degree. A lump supposed to be an absorbing subcutaneous abscess was first noticed when the child was 2. This may very well have been a case of sclerema, although the child was older than other recorded cases.

EXAMINATION OF THE CYST FLUID FROM CASE III

(a) *Fluid aspirated during life.*

The cyst over the right deltoid was aspirated without drawing any blood. About 1 c.c. of an oily pale straw-coloured liquid was obtained. Whilst drawing it into the syringe it was noted that there were minute white lumps in suspension in the oily fluid. These lumps quickly increased in size on cooling. They did not go back into solution until the fluid was heated to nearly 50° C. On examination of stained films under the microscope no cells and no organisms were seen. Cultures were not made. Under the polarising microscope the white lumps were seen to be masses of acicular anisotropic crystals, in every way similar in appearance to those seen in the frozen sections and ether extracts. The calcium content was 41 mgm. per 100 c.c. fluid, and the total cholesterol (colorimetric determination) was 1·5 per cent. (approx.).

(b) *Fluid obtained post-mortem.*

Post-mortem a number of small "cysts" were found scattered throughout the indurated subcutaneous fat of the arms, forearms, buttocks and thighs. These cysts were filled with a glistening white paste, closely resembling certain shaving or face creams. This paste had a peculiar odour which was pronounced as "camphoraceous" by several observers independently. (No injections of camphor had been given). Microscopically masses of anisotropic acicular crystals and oily globules only were seen.

DESCRIPTION OF PLATES.

Figure 1.
Photograph of Case III. showing the cystic swelling over the deltoid muscle.

Figure 2.
Frozen section of the subcutaneous tissue in Case I. Stained with Hæmalum and Sudan III. High power view showing the crystals.

Figure 3.
Microphotograph of a paraffin section of the skin and subcutaneous tissue in Case III. Low power view.

Figure 4.
High power view of the same section, showing the giant cells and the clefts from which the crystals have been dissolved out in the paraffin process.

Figure 5.
Case III. Paraffin section. High power view of an arteriole showing endarteritis.

Figure 6.
Case III. Frozen section examined under the low power with Nicol's prisms incompletely crossed. Shows a cyst and the anisotropic crystal masses.

Figure 7.
Case IV. Frozen section of subcutaneous fat under the low power with crossed Nicol's. Stained with Sudan III. Shows the anisotropic crystals lying free and in the fat globules.

Figure 8.
Frozen section of subcutaneous fat of a non-sclerematous (normal) infant. Low power. Crossed Nicol's. Sudan III. Shows the anisotropic crystals in the fat.

Figure 9.
Frozen sections, unstained. Polarising microscope: high power. Shows anisotropic crystals in sclerema and in a non-sclerematous infant's subcutaneous fat respectively.

Figure 10.
Anisotropic crystals in ether extracts of sclerema fat and normal fat respectively. Polarising microscope: 1/12 objective.

Figure 11.
X-ray photograph of upper limbs in Case III. Shows opaque deposits in subcutaneous tissues, and outline of a cyst.

Figure 12.
X-ray photograph of lower limbs in Case V. Shows similar deposits in subcutaneous tissues.

(Part II. will appear in next Issue.)

THE SPECIAL SCHOOLS OF LONDON.

BY

F. C. SHRUBSALL, M.D.

Although, unquestionably to the ailing child, the restoration of health and relief from crippling conditions are of supreme importance, experience has shown that when the necessary measures are spread over a period of years under such conditions as to limit the possibilities of education, still more if they are such as altogether to prevent formal education, the child is unduly handicapped on reaching the employable age. This difficulty became obvious so soon as universal elementary education was made the law of the land.

From the first the by-laws of the various school boards laid it down that ill-health was a reasonable cause of absence from school; but in time it appeared that there were numbers of children whose condition was such that education in an ordinary school was impossible over considerable periods, if not altogether. In 1893 an Act was passed allowing provision for special education for blind and deaf children, and in 1899 for those crippled, epileptic, or mentally defective. At first the arrangements were of permissive character, and were adopted only by some of the larger school boards. After the War such provision was made a duty in all areas in England and Wales. The problems thus raised differ in nature according to whether the area is urban or rural. In large urban areas there may be such a number of children suffering from similar defects and living within a reasonable distance of one another as to permit of the establishment of day-schools. In country areas where there may be only one or two defective children in the village, day-school provision is impracticable, and any children who are to be specially educated must be sent to residential institutions or boarded out in urban areas to attend suitable day-schools.

Of recent years, hospital schools have been established, in which active surgical treatment of certain defects can be carried on, while permitting of education in classes held in the hospital itself for certain hours of the day. The value of education in such a school, even if looked upon only from the standpoint of occupying the children's minds, has been thoroughly recognised as an aid to treatment. The value of the day-school has not always been equally recognised, though as time goes on the relations between medical and educational authorities have distinctly improved. The medical profession are, however, perhaps not fully cognisant of the facilities available, and thus a brief description of the arrangements in London may be of interest.

The London County Council provides facilities for the special education of those completely or partially blind, completely or partially deaf, for the physically or mentally defective, and for stammerers, and also secures places

in residential special schools for those suffering from frequent or severe epilepsy. Prior to admission to any of these schools, the children must be specially examined by the Council's consulting medical officers, who also visit the schools from time to time for the purpose of general medical supervision. These medical officers have been specially recognised by the Board of Education for the purpose, and on their statutory certificate the attendance of a child can be enforced by the Courts.

The Blind, Partially Blind, and Myopic.

In law a blind child is one who is "too blind to read the ordinary school books used by children," a definition which closely corresponds to that used for adults in the Blind Persons Act, viz., "so blind as to be unable to perform any work for which eyesight is essential." Children with impaired vision of all kinds are admitted so long as the disease is of a non-infectious character; and arrangements have been made with the Metropolitan Asylums Board to send children between the ages of 5 and 14, with chronic infectious conditions such as keratitis, blepharitis, trachoma, or ophthalmia, to residential country schools.

Blind children may be required to attend at special schools from the age of 5 upwards and are conducted to and from school by guides whenever this is necessary. The instruction in the schools for the blind includes the teaching of Braille and suitable forms of handwork occupations. At the age of 12 suitable children are transferred to residential schools for special trade training, and their attendance at such schools can be enforced until the end of the school term in which they attain the age of 16. Children who suffer from high and progressive myopia, or for other reasons should not strain their eyes, are admitted to the myope classes. These are small classes with specially-trained teachers, in which the ordinary methods of reading and writing are not employed, but the children read from large sheets with at least $\frac{1}{2}$-inch letters, and stand up to blackboards, so that writing is done at arm's length. Special attention is paid to mental work and the cultivation of "muscular" memory. Whereas in the ordinary school individual silent reading is encouraged, in the myope classes instruction is mainly by word of mouth, and the children go for oral instruction to adjacent elementary schools. Myopes as a rule leave school at the ordinary leaving age, the end of the term in which they become 14. Many myopic children are naturally studious and more prone than the ordinary child to read out of school, often from badly-printed material and in a poor light. The aim of the myope school is firmly to discourage reading other than from suitable type under suitable conditions; to avoid excessive and prolonged convergence during the early years of life; to encourage upright attitudes and to improve the general health. If the vision is so bad that work under these special conditions is impossible, the high myope needs to be educated by blind methods. No difficulty has been experienced with regard to those children who are completely or almost

completely blind, but in a certain number of instances ophthalmic surgeons have objected to the transfer of myopic children to the special classes.

The Deaf.

A deaf child is legally defined as one "too deaf to be taught in a class of hearing children in an elementary school." In schools for the deaf oral methods of instruction are used, special attention being paid to lip-reading and pronunciation. Special provision is made for the few oral failures in a residential school at Penn in Buckinghamshire, to which are also sent those who, in addition to being deaf, are also blind or mentally defective. About the age of 12-13 suitable children are transferred from ordinary schools for the deaf to residential schools for special trade training until they attain the age of 16. Deaf children may be admitted to school from the age of 5, but by law attendance cannot be enforced until the age of 7. It has, however, been found by repeated experience that the greatest advantage is derived from commencing special education at the earliest ages, and parents are therefore urged to allow their children to attend as young as possible. Special classes are provided in separate schools for those who are not quite deaf but are so far hard-of-hearing as to require special methods of education. The aim in these classes is to reinforce hearing by the acquisition of lip-reading; in consequence the children attend part-time in ordinary classes and are mixed as far as possible with those possessed of hearing in games and the like. As soon as they have acquired sufficient powers of lip-reading they are marked for transfer to an ordinary school. Both schools for the deaf and classes for the hard-of-hearing are visited daily by a nurse, who attends to discharging ears.

Physically Defective.

A physically defective child is defined as "one who is by reason of physical defect incapable of receiving proper benefit from instruction in ordinary public elementary schools but not incapable of education in a special school." The usual ground for admission is some cause of crippling or some organic disease which renders attendance at an ordinary school disadvantageous, but which might not prevent the child being safely educated in a small class under constant medical and surgical supervision. An ambulance service is provided to convey children who live at a distance from the school, or are unable otherwise to attend, but those who are physically fit and whose homes are so situated that they can walk to school or can travel by public conveyance are expected so to do. Provision is made for a certain number of recumbent cases in each school, and a trained nurse is constantly present to attend to the wants of the children. The schools are visited by the school doctor at least every four weeks, and there are also periodical visits by the Council's orthopædic surgeon. Attendance at these schools can only be enforced after the age of 7, but in certain circumstances younger children

may be admitted with the parents' consent, provided their attendance does not exclude a child of higher age. Attendance can be enforced up to the end of the term in which the child attains the age of 16. When, however, a physical defect is so far alleviated as to permit of a child undertaking the curriculum of an ordinary school with safety, arrangements are made for his transfer. The constant nursing and supervision available forms a very important link in the after-care arrangements of the hospitals since children are referred back for further advice and treatment whenever an adverse change occurs in their physical condition, or when any apparatus which may be worn becomes out of repair; while relatively small but not unimportant points such as the replacing of worn straps can sometimes be undertaken as part of the instruction in the school. Thus instead of a treatment instituted and continued for a time, then perhaps intermitted for several years, to be resumed only when a relapse or the increasing evidence of deformity has induced the parent to seek aid anew, the supervision is continuous, and further advice is available at the outset of any untoward occurrence.

The children at the school are fully occupied, playing under supervision, so that their activities are kept within safe bounds, and the general atmosphere is one of happiness and contentment. This point is stressed since occasionally practitioners are opposed to the transference of a child to such a school on the ground that it might make the child feel too much of an invalid, or that he might be affected psychically by being in company with other crippled children. Whilst perhaps it cannot be said that such results never follow, the present writer cannot recall having seen any such effects in a child who had attended for more than a few days at the school. This difficulty strangely enough is raised more particularly in relation to cases of heart disease, the very class of case in which the opportunity for graduated work, exercise, and play, and for recumbency, whenever this is necessary, affords the greatest benefits. The improvement in such children attending the special schools as compared with those who have been kept out of school altogether, or those who have been allowed to remain in the elementary schools on condition that they took part in no active exercise, is most marked. The majority of children attending schools for the physically defective are those who suffer from paralysis, quiescent tuberculosis of bones or joints, congenital deformities, or valvular disease of the heart. A certain number who have suffered from rheumatism or chorea may also attend, but usually only for temporary periods, as they are returned to ordinary schools as soon as their condition permits.

In former years tuberculosis took the largest place amongst the causes of crippling, but with the increased facilities in regard to residential hospital schools, and the resulting increase in the number of cures and in the rate of cure, the proportion in the day special schools has diminished. On the other hand, a larger number of cases of heart diseases following rheumatism are being admitted.

The numbers and ailments of those attending was shown in a recent survey to be as follows :—

Morbid Condition.

Tuberculosis—	
hip	506
spine	366
knee	253
other joints	113
various organs	23
Paralysis—	
poliomyelitis	943
hemiplegia and diplegia	210
other forms	36
Congenital deformities	239
Traumata	136
After-effects of rickets	235
Heart disease—	
congenital	216
acquired	707

At the date of the survey there was a total of 4,432 children on the rolls of the Physically Defective Schools. At the same date the total school population of the County of London was 697,882.

Children suffering from trivial deformities, epilepsy, or with discharges from sinuses which need frequent dressing, are not admitted. Cases of children suffering from chronic bronchitis, asthma, nephritis, some forms of anæmia, and similar conditions, require individual consideration. It is frequently found that their attendance is as irregular in a special school as it would be in an ordinary elementary school; there is little in the curriculum to confer special advantages upon them, consequently it often appears that attendance at an ordinary school near their home may be better than conveyance to a more distant special school. In such a case the school attendance department is, when necessary, informed that regular attendance cannot be expected.

Elder children are transferred to separate schools for trade instruction, and efforts are made to teach them trades adapted both to their physical defects and to the possibilities of securing employment in the district in which they live. It has been found that many can be placed in very advantageous situations. There are also a certain number of scholarships to provide courses of higher education for crippled, blind, or deaf children.

Open-Air Schools.

The day open-air schools provided in London for children from the age of 8 upwards are of two kinds; the first, for the debilitated and anæmic children, and those who may be suspected of a tendency towards tuberculosis

but in whom no definite signs of the disease have been detected; and the second, for those who suffer from definite pulmonary tuberculosis, or from tuberculous glands which have not broken down In the latter schools the children are visited by the tuberculosis officer for the district, who acts as a school doctor for this purpose. These children are conveyed to the schools on the Council's trams, and a nurse who is in daily attendance supervises meals, weighs, measures, and takes the temperatures of the children. Specified periods are set apart during which all the children rest on stretchers, and they are supplied with meals whilst at the school.

Besides the day open-air schools the Council has three residential open-air schools for non-tuberculous children who are slightly less debilitated than those who attend the open-air day school. The children stay at residential schools for some four to six weeks.

In addition to this, under the tuberculosis scheme, the Council makes arrangements for the treatment of children who need sanatorium care, whether for pulmonary or surgical tuberculosis.

Epileptic Children.

The Council has arrangements for dealing with children who suffer from chronic epilepsy of such a degree as to unfit them for attendance at an ordinary school, but whose mental state is such as to permit of their deriving benefit from education in residential epileptic colony schools, if they are between the ages of 7 and 16, subject to the parents' consent.

It will be realised, however, that to derive adequate benefit from these schools, the children should be sent at a relatively early age; attendance for the last year of school life is rarely of much avail. Attention is drawn to this point since again and again parents bring up children at the end of the elementary school period asking that they may be sent away and regretting that they have declined to take advantage of the opportunities offered at an early date.

There is a certain tendency among physicians to postpone a recommendation for residential treatment, and to keep the children for considerable periods out of school. While in many cases this is no doubt desirable, in others, regular occupation is an important element in treatment. It should be borne in mind that, although there are adequate facilities for dealing with children, the possibilities of dealing with the adolescent are very small, and education authorities are quite unable to assist in the task after the age of 16.

Stammering Classes.

Arrangements exist in certain parts of London for children of the age of 8 years and upwards who stammer, to attend for a course of three months at classes taken by specially-trained teachers. This course can be repeated if desirable.

MENTALLY DEFECTIVE CHILDREN.

A mentally defective child is legally defined as "one, who not being imbecile, and not being merely dull and backward, is by reason of mental defect incapable of receiving benefit from instruction in ordinary elementary schools, but not incapable by reason of such defect of receiving benefit from instruction in special schools or classes." Before a child who is attending an ordinary school is proposed for admission to such special school, he is seen by the school doctor and arrangements are made to secure the treatment of any defect such as poor vision, partial deafness, mouth-breathing, and the like, which might be responsible for his backwardness. If, after these have been dealt with as far as possible, no progress is made, the child is examined by certain school medical officers specially recognised by the Board of Education for the purpose. Generally speaking, the children admitted are those whose mental age as estimated by tests, both of the Binet-Simon pattern and by performance tests, amount to less than three-quarters of the normal, provided that they have in other ways shown themselves incapable of education in ordinary schools. In all special schools for the mentally defective there are small classes with specially-trained teachers and a specially adapted curriculum, whilst separate schools with special trade instruction are provided for elder children of either sex. If after admission to a special school a child is found to make such progress that he could be placed into Standard III. of an ordinary school, and shows sufficient powers of attention and reasoning to follow the work, he is re-transferred. If, on the other hand, after a considerable trial a child makes no progress either in the educational or occupational side, if his attention remains fleeting and his reasoning faculties do not develop, so that he appears to be incapable of learning to manage himself, he may have to be excluded as imbecile.

At the age of 15½ all children in the mentally defective special schools are reconsidered in the light of their mentality and home surroundings. Those who appear capable of fending for themselves harmoniously with others even in a humble capacity in the world, receive ordinary after-care for the purpose of placing out into employment until the age of 18, whilst those who are deemed to need institutional treatment or guardianship on account of their lack of intelligence, usually coupled with instability, are referred for care to the authority under the Mental Deficiency Act.

An important point with regard to the provision of special schools for the mentally defective is the further retardation which is caused by a sense of inferiority from which many such children suffer if allowed to remain in the classes of an ordinary school. Finding that they can never keep up with their fellows, they give up such efforts as they may have made and fall further and further behind. If transferred to small classes with their mental equals, and taught some subjects which they can demonstrate in their homes, *e.g.* the mending of boots, they learn that they may be of some use in the world, and receive praise instead of continual blame, to the great benefit of

their self-respect. There is no question that these schools may be regarded generally as schools of partial recovery. The word "partial" is used since the truly mentally defective remain so throughout their lives; but whereas without special training their condition is one of progressive deterioration, with special training in many cases better work can be got out of an initially inefficient mental mechanism to the benefit of the sufferer, his family, and the community at large.

The aim of the special schools is to get the best possible combination of treatment and education and to secure the utmost co-operation between the school medical service, private practitioners and hospital physicians and surgeons. Should any questions of difficulty arise the school medical officer always welcomes communications from his professional brethren, either directly or through the almoner's departments of the hospitals, since such would aid in the common task of removing the disabilities of the ailing child.

LAMBLIASIS AS A CAUSE OF CHRONIC ENTERITIS IN CHILDREN.

BY

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Intestinal infections due to the flagellate, lamblia intestinalis, attracted attention in England in the early years of the war when the disease first reached this country from the Eastern fronts. Since 1916, with the exception of Clifford Dobell's report[1], hardly any further reference to the disease has been made in English medical literature. I can find no clinical study of the infection published in this country though many papers on the subject have appeared in America.

This paper is based upon the study of 23 children infected with lamblia and has been largely written without previous reference to the publications of other observers. The conclusions reached are (1) that the infection is now by no means a rarity in hospital practice amongst children; (2) that it produces a chronic enteritis; (3) that the resultant diarrhœa is often severe enough to cause the subjects of the disease to be considerably below their proper weight, and occasionally will produce retarded development and diminution of growth, suggesting that in lambliasis we have a further possible cause of infantilism of the enteritic type; (4) that even in children true "carriers" may be found, infected with lamblia, but without symptoms.

Frequency.

Lamblia infections have only become common in England since the war. C. Dobell[1], reporting in 1920 on the occurrence of intestinal protozoa in the inhabitants of Great Britain, gave the carrier-rate of lamblia as 18-27% of people and states that the protozoon is especially common in the fæces of children. My colleague, H. Perkins[6], in 1921 examined for protozoa the stools of 120 children admitted consecutively to the medical beds at Paddington Green Children's Hospital. Lamblia was found in seven cases, a proportion of 5·8%. The inclusion of a considerable number of infants in this series probably makes the percentage of infected cases unduly low. In the last four and a half years lamblia has been found in the stools of 23 children who were under treatment at the hospital for intestinal disorders.

In my experience the infection is very much commoner in the children of the hospital class than in those dealt with in private practice. In a considerable number of fæcal analyses in the latter group I can only recall one case where lamblia was found, that of a child lately returned from Athens.

Sex and Age.

In the 23 cases, 14 were boys and nine girls, a proportion of rather more than three to two. All ages were represented: the youngest child yet found infected was 3 months old[2].

Symptoms.

Lambliasis in children may be found in three groups of cases :—

(1) True Carriers. It seems undoubted that even in children true carriers showing no symptoms of the infection may be found. Of the first series of seven cases already mentioned, three showed no intestinal symptoms at all. In this type the number of lamblia cysts found is very small, but whether this is due to the infection's being very mild or merely to the fact that the number of cysts evacuated is greatly increased during diarrhœa, I do not know.

(2) Mixed Conditions. Lamblia may be found in the stools of children suffering from other types of intestinal derangement. In the present series of cases it was found in one case of severe, relapsing and ultimately fatal dysentery, and the same association has been noted several times in adults. It was also present in two cases of cœliac disease, but it is evidently not common here as it has been discovered only twice in more than fifty cœliac cases. In one or two instances in the series lamblia has been associated with an excess of streptococci in the stools, but in the majority of cases the intestinal flora have been normal. I have not found lambliasis to be associated with, nor conducive to, abdominal tuberculosis.

From these results there seems no evidence that disorders of the intestine predispose towards infection by lamblia.

(3) Lamblia Enteritis. In the great majority of the 23 cases of this series the children were brought to hospital for chronic diarrhœa and no other explanation of this symptom could be found than the presence of lamblia in the stools, usually in very large numbers.

The diarrhœa persists for years, sometimes better, sometimes worse, but rarely completely absent even for a day. At the onset of the illness the number of stools may be as many as eight-twelve a day; later it is usually two-four daily; and after some years it may sink to one-two daily. As in all types of diarrhœa in children the bowels are apt to be moved directly after the taking of food. The diarrhœa is of the type associated with enterocolitis : the motions are loose, show the presence of all kinds of undigested food and a considerable quantity of mucus. Blood does not appear in the stools of uncomplicated lamblia cases. In some instances, owing to intestinal hurry and defective absorption, an excess of fat appears in the stools giving rise to a suggestion of cœliac disease. In seven cases of the present series the stools appeared fatty and were analysed for me by Dr. Perkins. The percentages of fat in them were as follows :—25·6, 24·8, 24·0, 22·8, 21·6, 17·2 and 10·6. These figures do not reach anything like the proportions of fat found in cœliac disease in its diarrhœic stages, but it is not improbable that in a young child with a rich milk diet, lamblia enteritis could produce stools containing a higher percentage of fat than these I have quoted. In one

instance of cœliac disease whose stools showed the presence of a few lamblia cysts, the percentage of fat in the dried fæces amounted to 63·2%. This figure was obtained when the diet was similar to that of the lamblia cases quoted above : on a low-fat diet, the percentage dropped to 22·0%.

The abdomen is usually prominent, but not excessively so. It looks the largest part of a thin child. The spleen is not enlarged and nothing abnormal can be felt within the abdomen.

Constitutionally these children, in the chronic stages, do not appear to be much poisoned or ill. They have none of the mentality of the chronic invalid child nor the peculiarities of the cœliac patient. They are lively enough and hungry. Their colour is usually good. They tend to be thin and considerably below the average weight for their age. The growth in height is retarded in some cases. In one curiously delicate child, very small at birth, the growth was said to have actually stopped. So far as I have been able to observe the development of these children, growth and development are not interfered with to anything like the degree which may obtain in cœliac disease. In this the dwarfing is a toxic effect and may be very severe : in lambliasis it appears in milder degree and is due to deprivation only.

I quote the two cases of the series in which diarrhœa had lasted for the longest time, namely, ten and eight years respectively :—

Robert H., born September, 1911. In 1915 had a severe attack of diarrhœa which produced drowsiness and thirst. The diarrhœa has continued ever since. The bowels act three or four times a day, especially when food is taken. He has wasted a little and his growth has been slow. Measles in 1915; scarlatina, 1917. October, 1920, was first seen. Height 47 ins. (average for age, 50 ins.). Weight, 52 lbs. 6 ozs. (average, 60½ lbs.). Secondary dentition represented by only one upper and two lower central incisors. Abdomen enlarged; nothing abnormal felt. Stools, two-four daily, contain much undigested food; striated muscle fibre; mucus; no excess of fat (10·8% of dried fæces); very many lamblia cysts. Gained some weight as an in-patient for four weeks. 1923. Acute appendicitis; appendix removed without having any effect on the diarrhœa. July, 1925. Now nearly 14 years old. Still has diarrhœa persistently, but it is much less than formerly, not often more than two motions a day. Abdomen is slightly full in appearance. The boy looks well; is thin, but very active and wiry; boxes and swims. Is growing faster. Height, 58⅛ ins. (average, 59⅛ ins.). Weight, 82½ lbs. (average, 92 lbs.).

Evidently here the symptoms are now tending to subside and the harm done to become less; normal height has been nearly attained.

Kathleen J., born October, 1912. Diarrhœa and enlarged abdomen since 1917; has attended many doctors for these two symptoms. In October, 1921, was notified as "tuberculous bowels"; bowels then acted five-six times daily, motions pale, offensive, liquid, large, contained mucus, but never blood. In September, 1923, she was referred to me as a possible case of cœliac disease. She was then obviously stunted in growth, her weight was 55 lbs. 2 ozs. (average for age, 68 lbs.). The abdomen was prominent. She had a high colour and her general condition was good. She was passing three-four stools daily. Stool report by Dr. Perkins: "Does not look like a cœliac stool, much undigested food, mucus, great numbers of lamblia cysts; fat 17·2% of dried fæces; flora normal." July, 1925. Still has two-three stools daily. She looks very well, has a high colour. Shows no mammary development. Height 51¼ ins. (average for age, 57 ins.). Weight, 64½ lbs. (average, 84 lbs.).

The effect of the infection on the heights and weights of some additional unselected cases is shown in the following table :—

Case No.	Age.	Length of Diarrhœa. Years.	Comparison with Normal. Height. Inches.	Comparison with Normal. Weight. lbs.
1	$9\frac{1}{2}$ 14	5 10	-3 -1	-8 $-9\frac{3}{4}$
2	11 $12\frac{3}{4}$	$6\frac{1}{4}$ 8	? $-5\frac{3}{4}$	$-12\frac{7}{8}$ $-19\frac{1}{2}$
3	$3\frac{3}{4}$ $5\frac{1}{2}$	$3\frac{1}{4}$ 5	$-1\frac{1}{2}$ $-2\frac{1}{2}$	-5 $-6\frac{7}{8}$
4	11	3	$-4\frac{5}{8}$	-19
5	$9\frac{1}{2}$	2	$-1\frac{3}{8}$	$-12\frac{1}{2}$
6*	12	$2\frac{1}{2}$	-9	$-31\frac{1}{4}$
7	11	$1\frac{1}{2}$	$+\frac{1}{2}$	-7
8	4	?	-4	-13

* Very small from birth : has stopped growing : same size as sister aged 9.

Complications.

In the series of 23 cases, one developed prolapse and another acute appendicitis. Both these conditions are such as might be expected to arise in persistent enterocolitis in children.

Diagnosis.

In cases of long-lasting diarrhœa in children where examination shows no other abnormality than a heavy infection by lamblia, it is not unreasonable to assume that this is the cause of the symptoms. Such cases as have been detailed above are of a peculiar type; for diarrhœa to last for eight or ten years in early life has been hitherto a very unusual thing and such cases are well explained by the fact that lamblia infections are much less uncommon now than formerly. These cases bear but the most superficial resemblance to those of abdominal tuberculosis and can easily be distinguished from bacterial infections of the dysenteric types; nor are they like instances of nervous diarrhœa.

It is worth pointing out that as far as the *history* of illness goes, the lamblia infection resembles cœliac disease more than any other disorder. In both conditions there is a history of persistent diarrhœa, some enlargement of the abdomen and retardation of growth, although the symptoms are usually far more severe and the invalidism far greater in cœliac disease than in lambliasis. Further, the similarity between the two conditions may be increased by the fact that from time to time stools apparently containing an excess of fat may occur in the lamblia cases. I have several times sent fæcal specimens to be analysed on the suspicion of the presence of cœliac disease and received back a report of lamblia infection. If the stool is examined there is little difficulty in distinguishing between the two conditions. Besides the presence of the protozoon the lamblia stool is that of a chronic entero-colitis. It contains much undigested food and mucus and perhaps is slightly fatty. In cœliac disease the great abnormality is the excess of fat without evidence, or without persistent evidence, of enteritis or any corresponding degree of maldigestion of the non-fatty foodstuffs[5].

A comparative study of lamblia cases with cœliac cases will convince the observer that cœliac disease is not due to an entero-colitis, in spite of the superficial resemblance of the symptoms in the two groups of cases.

Course and Prognosis.

As I have already stated the infection by lamblia does not produce any serious degree of illness, though it causes wasting and retarded growth. The diarrhœa seems to be at its worst at the onset of the infection and to persist for many years with some degree of severity. As time passes the diarrhœa tends to diminish until at last it ceases to be even an inconvenience. The infection, however, appears to persist throughout childhood.

It is probable that the most harmful effects of the infection occur in the youngest subjects. I certainly do not agree with those authors who state that the infection is harmless; as far as children are concerned this is untrue.

Treatment.

Claims have been made for various drugs that they are capable of ridding the intestine of lamblia. In no case have such claims been substantiated. Lately an arsinic preparation, Stovarsol, has been credited with this power by Marchoux[3] [4], but this is frankly denied by Gillmore[2]. The drug is given by the mouth and is easily administered to children. I have had no success in my trial of it. Ordinary disinfectants appear useless.

It has to be remembered in connection with all claims to cure lambliasis that the flagellate will spontaneously disappear for a time from the stools. Tests to be of conclusive value should be made on several consecutive days after the daily administration of saline purges. Up to the present no drug appears to have passed such a test as this.

Where the diarrhœa is doing sufficient harm, improvement can be quickly brought about by such measures as rest, colon lavage, careful dieting and the administration of bismuth, with or without opium.

My thanks are due to my colleague, Dr. T. Pearse Williams, for access to some of his cases; to Dr. R. King, Medical Officer of Health for Ilkeston, for the after-history of the second case quoted here; and to Dr. H. Perkins for his numerous pathological reports.

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THE REMOTE PROGNOSIS OF EMPYEMA IN CHILDREN.

BY

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The immediate prognosis of empyema in children has been shown by Cameron and Osman[3] to depend entirely upon wnether it is syn-pneumonic or meta-pneumonic. The former should not be operated upon by the removal of a rib and with an anæsthetic until the termination of the pneumonic process. The latter, on the other hand, may be submitted to operation at once.

The best surgical procedure for dealing with this disease is the subject of constantly recurring discussion,[4] [5] [8] [1] but the ultimate prognosis does not appear to have received the attention it warrants.

The term " cured " when applied to an empyema after operation seems a very wide one. It is exceptional to find any case discharged from hospital as otherwise. It seems that only such as have a persistent discharge from the wound, or failure of expansion of the lung, or other similar severe disability are not so regarded.

The only reference I have been able to find to the remote effects of this disease after operation is an investigation of 146 cases by Saltzman and Sievers[7]. Their patients had been operated upon between 20 and 40 years previously. These observers limited their attention to the increase of life insurance risk and the question of the subsequent development of tuberculosis. Their series showed a moderately increased mortality rate, mainly limited to cases between 19 and 25 years of age at the time of operation, but the tuberculosis death rate did not show any increase over that of the whole country. The analysis was made on information received.

My attention was first drawn to this question by encountering one or two cases with severe pulmonary disability consequent upon a previous operation for empyema. This it was which led me to conduct the following enquiry.

During 1913, 1914 and 1915, 71 cases of empyema were discharged as cured, after operation, from the Children's Hospital, Birmingham. As the average duration of the symptoms of these children before operation was 4·8 weeks, the shortest being two weeks, they may all be classified as of meta-pneumonic type. In all rib resection was the operative procedure adopted, and the stay in hospital after operation averaged 6·2 weeks. Fifty-three of these children have been traced during the past few months, and I have personally examined 36 of them.

My observations are based on this series.

Regarding in the first place those 17 that have not been seen, definite information has been obtained from 12 that their health is and has been satisfactory in every way. One child has spent nearly two years in a sanatorium suffering from tuberculosis of the hip joint, apparently without any pulmonary lesion. The remaining four children have died—one from scarlet fever, but the cause in the other three could not be ascertained; one dying a few months, one 12 months, and one two years after operation.

The mortality rate, therefore, taking into consideration only those cases traced, is 7·5%. Further, in none of these can the empyema definitely be blamed as the cause of death.

As stated above, 36 children have personally been examined at an interval of from 10 to 12 years after an operation for empyema. The youngest of these was one year and two months at the time of operation, and the large majority (viz. 22) were under 4 years of age.

The excellent state of the general physical condition of these children has been an outstanding feature. In fact, in only three was the physique in any way below average. Another remarkable fact that has emerged from this investigation has been the almost complete immunity from respiratory diseases these children have enjoyed, none having afterwards suffered from asthma, pneumonia or another empyema, etc., and only a minority from coughs and colds.

No child subsequently developing pulmonary tuberculosis has been found. Three cases, it is true, have spent a short period in a sanatorium; one for six weeks in 1915, one for six weeks in 1918, and one for three months in 1923. My examination of these three did not reveal any evidence of tuberculous infection, the physique was good, there were no symptoms and the physical signs of fibrosis were of minor extent and of basal situation. Moreover, the clinical findings were supported by the radiological appearances. Probably these children were admitted to a sanatorium for observation; if the suspected diagnosis had been confirmed they would certainly have been detained for considerably longer periods.

Most writers on this subject record a certain number of cases in which a second operation has been found necessary, either for a discharging sinus or for a necrotic rib. Brown[2] found 10·5% in 171 cases, and Pybus[6] had 7% in 100 cases requiring such further treatment. There were two cases (3·8%) in my series.

One child had its first operation for a left empyema in 1911. The wound broke down and 18 months later, in 1913, she was re-admitted to hospital and a second operation performed. She then remained well for two years when discharge again recurred. A third operation was performed in 1915, since when there has been no further trouble. When I saw the girl 14 years after the first operation and 10 years after the last, now aged 15 years, she

looked well but pale. The left side of the chest measured an inch less than the right, but its expansion was almost as much as that of the right. There was clinical evidence of local fibrosis around the scar, but nothing further. The heart was not displaced, and she had no scoliosis.

The other case was another girl first operated upon in 1914 for a right sided empyema. From 1915 to 1923 there was a constant discharge from the wound. During the latter year she was re-admitted to hospital and a second operation successfully performed. She is now a fine strong healthy looking girl; the right shoulder was carried at a lower level than the left and the right chest measured three quarters of an inch less than the left and had practically no lateral expansion. There were signs of diffuse bronchitis throughout both lungs, but no bronchiolectasis and no scoliosis. A remarkable result in view of the fact that she had had a constant discharge for eight years.

Two further cases related some delay in the healing of the wound or some further discharge. In both the information was vague, medical attention was not necessary, and both showed but slight fibrosis though, in addition, some lateral curvature of the spine.

That so serious an intra-thoracic lesion as an empyema should heal to leave behind no trace of its occurrence is difficult to comprehend. Yet, in 25% (nine) of my cases the only physical signs remaining were those of the slightest fibrosis confined to the immediate neighbourhood of the scar, there was no deformity of the chest wall, no spinal curvature and the two sides of the chest were of equal measurement at expiration and at inspiration. Though the remaining 75% all showed some deviation from the normal, the degree of change was much less than would be expected. The two sides of the thorax were of equal measurement at rest in four cases, but there was a limitation of expansion of the affected side. In a further six cases, whilst the measurement of the two sides of the chest was unequal on expiration, the affected side showed as good an expansion as the healthy one.

Thoracic deformity in combination with a deficient expansion on the side of the operation was noted in 12 cases (33·3%). These inequalities, however, were only of very slight extent. In seven the difference in measurement at expiration was under an inch, and the maximum difference of one and a half inches was present in only two cases. The diminution of expansion of the affected lung in all was very small, and in the majority could not have been detected without the aid of a measuring tape.

No child gave any symptoms or showed any physical signs to warrant a diagnosis of bronchiectasis or bronchiolectasis of even the mildest degree.

Radiological examinations of the chest were carried out in every case. These merely served to confirm the clinical findings. Practically every case showed some increase in hilum shadows, usually but not always more marked in the affected lung. In addition a few showed a limitation of movement of the homolateral side of the diaphragm.

The examination of 36 children 10 to 13 years after operation for an empyema leads me to the opinion that the remote prognosis is excellent, though the number is much too small to permit of more than a provisional judgment. All show some evidence of scarring of the lung, but it is of negligible extent. So far as I have been able to determine, there is no factor which will enable any forecast of the degree of this fibrosis to be made. The duration of the disease prior to operation gives no assistance, nor does the time required after operation for the healing of the wound; in fact, the average duration of symptoms before operation and the subsequent stay in hospital of my group showing no clinical fibrosis was practically identical with those averages obtained from the whole 36 cases. To quote the extreme case, this was a boy who had had pneumonia 10 weeks before admission to hospital, he was kept 11 weeks after operation and yet recovery has, to all intents and purposes, been perfect.

I am indebted to Mr. F. A. R. Stammers for his kind assistance in collecting these cases, and I have to thank Dr. G. A. Auden for tracing some of the children.

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NEPHRITIS IN CHILDREN AND ITS PROGNOSIS.

BY

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Being in some doubt as to the prognosis of nephritis in childhood, and hesitating to base our beliefs upon observations of too short a duration, we have endeavoured to form our conclusions on this subject from a more protracted investigation. With this object in view we have followed up 64 cases, all of which have been re-examined at least twice in a period of three and a half to five and a half years after the onset of the renal symptoms.

The majority of our cases were first observed in the acute stages, so that an attempt has been made to classify them by the symptoms which they then presented. Subsequent examinations have served to show in which type of acute nephritis the largest proportion of recoveries can be expected.

Classification and Symptomatology of Acute Cases.

For the purposes of this paper acute nephritis in children has been divided into two main groups, the parenchymatous or "exudative," and the hæmorrhagic. Parenchymatous is taken to include all cases of tubulo- and glomerulo-nephritis, post-scarlatinal nephritis being the best known example of the latter. It is not intended to discuss these two sub-groups separately, as symptomatically they present essentially similar features, and in the clinical state it is usually a matter of conjecture whether the glomeruli or the tubules are chiefly affected. In either case the urine is blood stained at the onset of the illness, and traces of blood may be detected either microscopically or chemically for several weeks afterwards. The quantity of albumen passed is usually considerable, and is much in excess of that attributable to the amount of blood present in the urine. Casts, granular, epithelial, and hyaline are numerous, and blood casts may also be found. A variable degree of oliguria is common in the early stages, the obstruction to the urinary outflow resulting either from swelling of the endothelium lining the capillaries of the Malpighian tufts, or from blocking of the tubules by cellular debris. Other symptoms often associated with acute parenchymatous nephritis are headache, vomiting, abdominal pain, a slight rise of temperature, and œdema. Œdema is the most constant symptom of this type of nephritis, very often becomes generalised, and is not infrequently the only indication of the occurrence of the renal trouble.

Acute hæmorrhagic nephritis[6] on the other hand can usually be distinguished from the above type. Its chief characteristic is the sudden onset of hæmaturia, in most cases without reduction in the quantity of urine passed. The hæmaturia occurs during, or follows at a short interval after, some acute or subacute infection, especially of the naso-pharynx. There may be little or no evidence of constitutional disturbance when the hæmaturia commences during the subsidence of the primary infection, but in those cases where the two conditions exist synchronously general symptoms such as headache, vomiting, abdominal pain and pyrexia are often present. The quantity of blood passed is greater than in the acute parenchymatous type, and the colour of the urine may vary in the initial stages between the bright red of arterial blood and a " smoky " brown. The albumen present can largely be accounted for by the degree of hæmaturia. In many cases the blood and albumen disappear almost synchronously from the urine in a few days or weeks, but may persist sometimes intermittently for several weeks. It is not uncommon, however, for a trace of albumen to be present in the urine for a considerable time after the passage of red blood corpuscles has ceased. It is important to note that œdema is seldom generalised, and in most cases consists of no more than a slight puffiness round the eyes. Blood and other casts are met with, but are not so numerous as in the parenchymatous type.

As a rule in hæmorrhagic nephritis there is no increase of cardiac dulness nor of the blood pressure, the blood urea is not raised, and the power to concentrate urea is within normal limits. In parenchymatous nephritis, on the other hand, a disturbance of one or other of these features is commonly present in the acute stages.

Ætiology.

As to the causation of acute nephritis the belief is growing that it is more commonly secondary to some naso-pharyngeal infection, especially tonsillitis, than to any other cause. Streptococcal infections appear to be the commonest precursors of acute nephritis, but pneumococcal and staphylococcal infections must also be mentioned. In the parenchymatous type the presence of toxins in the circulation is generally held responsible for the renal injury. In the hæmorrhagic type, on the other hand, it is possible that the condition is of embolic origin affecting a proportion of the glomeruli in a scattered uneven manner. This type of nephritis is described by Muir[3] as a complication of subacute endocarditis due to streptococci. Allison[1] in making some observations on acute nephritis in children was impressed by the sudden appearance of hæmaturia in several of his cases, and suggested infarction as a cause. Cultures of the urine, which were made in six of our hæmorrhagic and in seven of our parenchymatous cases, were all negative.

While parenchymatous nephritis frequently occurs without any apparent cause, yet in hæmorrhagic nephritis it is possible in most cases to associate the condition with some definite focus of infection. In the present series of 64 cases, 49 were examples of acute nephritis, and of these 22 were classified

as parenchymatous, and 27 as hæmorrhagic. In only two of the hæmorrhagic cases could no focus of origin be traced, while in nine of the parenchymatous cases the causation was quite obscure. Table I. shows the nature and proportion of the probable causes in each group.

TABLE I.

Analysis of Infective Conditions associated with 49 cases of Acute Nephritis.

Parenchymatous.		*Hæmorrhagic.*	
Tonsils found enlarged	5	Tonsillitis or large unhealthy tonsils	7
Cervical adenitis	1	Tonsillitis and chorea	1
Scarlet fever	4	Cervical adenitis and tonsillitis	9
Measles	1	Otitis media	6
Gastro-enteritis	1	Pneumonia	2
Bronchitis	1	Origin obscure	2
Origin obscure	9		
Total	22	Total	27

The figures in the above table suggest that tonsillar infections and associated conditions such as cervical adenitis and otitis media are of more importance in the causation of the hæmorrhagic than of the parenchymatous type of nephritis; 85·5% as compared with 27·2% in the present series. The proportion of cases in the two sexes was fairly evenly distributed; 11 boys and 11 girls in the parenchymatous type, and 15 boys and 12 girls in the hæmorrhagic. As regards the age incidence in our series all the hæmorrhagic cases occurred between the third and tenth years, 16 being between the third and fifth years. The majority of the parenchymatous cases occurred between the third and eleventh years, while seven were between the ages of one and three. Nine cases occurred in the period three to five.

Clinical Features of Each Group.

Some of the main features in each group of 22 cases of parenchymatous and 27 cases of hæmorrhagic nephritis are given in tabular form in Table II.

TABLE II.

Œdema :—	*Parenchymatous.*	*Hæmorrhagic.*
Generalised	14	2
Slight general	3	3
Legs swollen	1	1
Face swollen	2	9
No œdema	2	12
	22	27

Albumen present on discharge ...	13	7	
,, absent ,, ...	5	20	
	18	27	
Heart enlarged	6	2	(1 chorea)
Optic neuritis	1	0	
Deaths	4	0	

Table II. clearly shows the greater tendency to œdema in the parenchymatous type, as in the nine hæmorrhagic cases marked " face swollen " there was only some puffiness round the eyes. The length of stay in hospital for the cases of the parenchymatous type was roughly one to five months, while that for the hæmorrhagic cases was relatively shorter. A trace of albumen was present in the urine in seven cases of the latter type when discharged, while in 13 of the parenchymatous type albumen was present on leaving hospital in quantities from a trace to a fairly dense cloud. In about half of the hæmorrhagic cases the blood and albumen disappeared from the urine almost simultaneously, and in only one were red blood corpuscles still found on microscopical examination when the patient left hospital. This case (W.B.) will be referred to again. Allowing for the number of days elapsed after the onset of symptoms before the patients entered hospital the urine remained obviously blood stained for a rather longer time in the hæmorrhagic cases, and microscopically red blood corpuscles were found in the urine for one week to three months; three weeks in 12 cases. In the parenchymatous cases, also, erythrocytes were present any time up to three months, but more often were absent after a few days, and in five cases no red cells were seen at all while in hospital.

Among the parenchymatous cases four are included in which a recent history of scarlet fever was obtained, all of which showed general œdema, and a trace of albumen was still present at the time they left hospital.

Other Forms of Nephritis in Series of 64 *Cases.*

(B) Chronic Parenchymatous Nephritis. Eight cases were encountered which had already passed into the chronic state, including two cases of scarlatinal origin. Two were without œdema, and the other six had generalised œdema. The albuminuria was persistent in all. In five of the eight cases red blood corpuscles were present in the urine, often in considerable quantity, during exacerbations of the renal trouble.

(C) Syphilitic Nephritis. There were four examples of this type, in each of which the Wassermann reaction of the blood was positive. One was 4 months and two 6 months old, and albuminuria and œdema had been present from two weeks to two months. All died except the fourth case, a child of $5\frac{1}{2}$ years with a slightly positive Wassermann reaction, who had had

œdema and albuminuria intermittently for two years. Her mother had a strongly positive Wassermann reaction.

(D) Chronic Interstitial Nephritis. There were two cases of this type. Both showed bony changes of the character met with in renal dwarfism[4]. Their ages were 4½ and 6 years. Frequency of micturition with a low specific gravity of the urine (1006-1008) was present in both instances, and their blood ureas were 108 and 76 mgm. per 100 cc. respectively. Both showed an increase in the area of cardiac dulness and a diminished urea concentration power (below 2·0).

(E) Stone in the Kidney. The following case has been included as the history resembles in many ways that of a case of hæmorrhagic nephritis. A boy of 6 had intermittent attacks of hæmaturia for four months, each attack being accompanied by pain in the back. At the time of examination the urine contained albumen, a few red blood corpuscles and one or two casts per field. Radiographic examination for calculus was negative. His subsequent history discloses that a year after leaving hospital he passed a stone in the urine with much pain, and three years later was stated to have had no further renal trouble.

Results of Re-examination.

(A) Tables III. and IV. give the results of examinations of the cases of acute parenchymatous and hæmorrhagic nephritis at three and a half to five and a half years after the onset of the symptoms.

TABLE III.

Re-examination of 18 Surviving Cases of Parenchymatous Nephritis.

Case.	Dates.	Urine.	B.P. Heart enlarged = †	Maximum Urea Conc.	Remarks.
J. W.	1920	Alb. trace	—	—	Pallor, puffy face
♀	1922	Alb. 0	B.P. 100	—	Looked healthy
16 years	1925	Alb. trace Cells +	B.P. 118	3·12	Drowsy and languid
J. P.	1922	Alb. 0	B.P. 100	—	Tonsils + +
♂	1925	Alb. v.s t.*	B.P. 103	3·6	Looked healthy
9 years		Cells +			
J. B.	—	—	—	—	Died
♀					
8½ years					
A. G.	1922	Alb. + + +	B.P. 120	2·1	Sometimes puffy
♀	1925	Alb. + + +	B.P. 120	2·9	Looked healthy
15 years		Cells			

* alb. v.s.t. = very slight trace albumen.

TABLE III.—*continued.*

Case.	Dates.	Urine.	B.P. Heart enlarged = †	Maximum Urea Conc.	Remarks.
J. B. ♂ 11 years	1922 1925	Alb. trace Alb. v.s.t.* Cells +	B.P. 120 B.P. 110	— 4·0	Face puffy Pallor, short of breath
F. H. ♂ 10 years	1922 1925	Alb. 0 Alb. v. s. t.* Cells	B.P. 120 Heart† B.P. 110	— 3·5	Œdema legs Developed hepatic cirrhosis
C. L. ♀ 7 years	1922 1925	Alb. 0 Alb. v. s. t.* Cells	B.P. 93 Heart†	— 3·2	Looked healthy Looked healthy
G. G. ♂ 15 years	—	—	—	—	Died
J. D. ♂ 11 years	1922 1925	Alb. 0 Alb. 0	B.P. 110 B.P. 90	— 3·9	Looked healthy Looked healthy
L. S. ♂ 13 years	1922 1925	Alb. 0 Alb. 0	Heart† B.P. 120 Heart†	— 3·3	Puffy Looked healthy
E. P. ♂ 12 years	1922 1925	Alb. + + Alb. + + + Cells +	B.P. 110 Heart† B.P. 140	2·6 2·6	No complaints Looked healthy
V. C. ♀ 12 years	1922 1925	Alb. 0 Alb. + + + Cells +	Heart† Heart†	— 2·4	Very pale Looked healthy
F. L. ♀ 8 years	1922 1925	Alb. 0 Alb. 0	B.P. 80 B.P. 120	— 2·8	Looked healthy Looked healthy
J. H. ♂ 11½ years	1922 1925	Alb trace Alb. v.s.t.* Cells +	— B.P. 120	— 3·3	Looked healthy Looked healthy
H. P. ♂ 6 years	1922 1925	Alb. + + Alb. 0	B.P. 80 B.P. 90	— 3·4	— Looked healthy
F. B. ♀ 7 years	1922 1925	Alb. 0 Alb. 0	— B.P. 90	— 3·4	Looked healthy Looked healthy
L. L. ♀ 14 years	1922 1925	Alb. trace Alb. + Cells +	B.P. 110 B.P. 105	2·0 3·1	— Puffy in mornings
P. W. ♀ 5½ years	1925	—	—	—	Too ill to come to hospital. Headaches and vomiting

* alb. v.s.t. = very slight trace albumen.

TABLE IV.

Re-examination of 27 Cases of Hæmorrhagic Nephritis.

Case.	Dates.	Urine.	B.P. Heart enlarged = †	Maximum Urea Conc.	Remarks.
J. D.	1922	Alb. 0	—	—	Looked healthy
♂	1925	Alb. 0	B.P. 100	—	Looked healthy
12½ years					
D. K.	1922	Alb. 0	Heart†	—	Chorea
♀	1925	Alb. trace	Heart†	3·2	Chorea
16 years		Cells +	B.P. 85		
A. N.	1922	Alb. 0	—	—	Looked healthy
♀	1925	—	—	—	Looked healthy
11 years					
G. A.	1922	Alb. 0	—	—	Looked healthy
♀	1925	Alb. 0	B.P. 105	3·4	Looked healthy
16 years					
B. C.	1922	Alb. 0	—	—	—
♀	1925	—	—	—	Intermittent hæmaturia (not seen)
9 years					
J. D.	1922	Alb. 0	—	—	Looked healthy
♂	1925	Alb. v.s.t.*	B.P. 85	—	Looked healthy
9 years		Cells +			
H. H.	1922	Alb. 0	—	—	Looked healthy
♂	1925	Alb. 0	B.P. 110	2·9	Looked healthy
9½ years					
W. W.	1922	Alb. 0	—	—	Looked healthy
♂	1925	Alb. 0	B.P. 110	3·19	Looked healthy
8 years					
A. R.	—	—	—	—	Died. T.B. Meningitis
♂					
14 years					
E. E.	1922	Alb. 0	B.P. 100	2·7	2 attacks hæmaturia,
♂	1925	Alb. 0	B.P. 100	3·15	cystocopy negative
15 years					Looked healthy
N. P.	1922	Alb. 0	B.P. 100	—	Looked healthy, hæmaturia before tonsillectomy 1923
♀					
8½ years	1925	Alb. v.s.t.*	B.P. 120	2·8	Looked healthy
		Cells +			
M. F.	1922	Alb. 0	B.P. 100	—	Thin child
♀	1925	Alb. s.t.**	B.P. 130	3·3	Delicate
13 years		Cells +			
T. B.	1922	Alb. 0	—	—	Looked healthy
♂	1925	Alb. 0	B.P. 90	2·7	Looked healthy
7½ years					

* alb. v.s.t. = very slight trace albumen.
** alb. s.t. = slight trace albumen.

TABLE IV.—*continued.*

Case.	Dates.	Urine.	B.P. Heart enlarged = †	Maximum Urea Conc.	Remarks.
A. B. ♀ 7 years	1922 1925	Alb. 0 Alb. trace Cells +	— B.P. 90	— 2·8	Looked healthy Looked healthy
B. S. ♀ 7½ years	1922 1925	Alb. 0 Alb v.s.t.* Cells +	— B.P. 120	— 3·7	Looked healthy Looked healthy
J. T. ♂ 13 years	1922 1925	Alb. 0 Alb. 0	— B.P. 120	— 3 8	— Looked healthy
W. B. ♂ 9 years	1922 1925	Alb. + Alb. + + Cells + +	— Heart† B.P. 105	2·3 1·6	Delicate Blood urea 53 Unhealthy
E. C. ♂ 8 years	1922 1925	— Alb. 0	— B.P. 85	— 3·24	— Looked healthy
G. W. ♀ 10 years	1922 1925	Alb. 0 Alb. trace Cells +	B.P. 80 Heart† B.P. 110	— 3·75	Tonsils + + Rheumatism
H. H. ♂ 14 years	1922 1925	Alb. 0 Alb. trace	B.P. 110 B.P. 110	— 3·1	Looked healthy Looked healthy
B. B. ♂ 9 years	1922 1925	Alb. + Alb. trace Cells +	B.P. 90 B.P. 108	— 2·5	Occasional vomiting Looked healthy
F. S. ♀ 7 years	1925	Alb. 0	B.P. 90	3·2	Looked healthy
F. T. ♂ 10 years	1922 1925	Alb. 0 Alb. 0	 B.P. 120	— 3·6	Looked healthy Looked healthy
A. V. ♂ 6½ years	1922 1925	Alb. 0 Alb. v.s.t.*	B.P. 110 Heart† B.P. 110	— 3·06	Looked healthy Otorrhœa, looked healthy
P. O. ♀ 8 years	1922 1925	Alb. trace Alb. v.s.t * Cells +	— B.P. 80	— —	Looked healthy Looked healthy
D. C. ♀ 10 years	1922 1925	Alb. 0 Alb v.s.t.* Cells +	B.P. 95 B.P. 90	— 4·03	Looked healthy Looked healthy
J. M. ♂ 13 years	1922 1925	— Alb. + Cells +	— Heart† B.P. 130	— 2·5	— Looked delicate, easily tired

* alb. v.s.t. = very slight trace albumen.

A few comparisons of the after-results in the two types of acute nephritis, parenchymatous and hæmorrhagic, are worthy of separate mention.

1. Recoveries. Good physical condition and an absence of abnormal constituents in the urine—five parenchymatous and 10 hæmorrhagic. Two further cases of hæmorrhagic nephritis might be added to the list of recoveries, as although a trace of albumen was present there was no cellular deposit. As regards the presence of a slight trace of albumen in the urine we consider it of negligible importance except when accompanied by an abnormal number of leucocytes and epithelial cells in the centrifugalised deposit. The presence of an abnormal number of these cells in addition to a small trace of albumen is evidence in our opinion of renal damage.

2. Apparent good health, but with abnormal urinary constituents, consisting of albumen, a " very slight trace " to a dense cloud, and white blood corpuscles in the centrifugalised deposit—six parenchymatous and nine hæmorrhagic. In the latter group red blood corpuscles were present in only two, and the albumen did not amount to more than a trace in any of the nine cases. Three of the parenchymatous cases had enlarged hearts, and two of the hæmorrhagic, but both of these had developed rheumatism since the onset of the nephritis.

3. Deaths. Two of the parenchymatous cases had died of chronic nephritis, making a total of six deaths in the original group of 22. One hæmorrhagic case had died, but the cause of death was tuberculous meningitis.

4. The five remaining parenchymatous cases presented obvious signs of chronic nephritis. Of the remaining five hæmorrhagic cases one had had recurrent attacks of hæmaturia (one was not seen), and three looked unhealthy and had red blood corpuscles in the centrifugalised urinary deposit. One of these—W. B. already referred to—is worth mentioning in fuller detail, being a case which presented at the onset all the features of the hæmorrhagic type of nephritis. Subsequently he had frequent occurrences of hæmaturia with a gradual loss of health, cardiac hypertrophy and a diminishing power to concentrate urea, the final figure being 1·6. He had never been œdematous. When last seen the blood urea was 53 mgm. per 100 cc., and casts were present in the urine. This case demonstrates the possibility of the hæmorrhagic form developing into the chronic, possibly interstitial, type of nephritis.

5. Of the four post-scarlatinal cases included in the parenchymatous group two showed complete recovery and two had become chronic.

6. The figures for the urea concentration test performed in 21 of the parenchymatous cases and in 15 of the hæmorrhagic were all above or at the normal level (2·5), except in one case in each type.

(B) *Chronic Parenchymatous Nephritis.*

Four out of eight cases had died. Of the remainder only one appeared healthy, but had an enlarged heart and albumen and cells in the urine. The other three were obvious chronic renal cases; one had a blood urea of 119 mgm. per 100 cc., and urea concentration 1·3. Otherwise the urea concentration figures were above 3·0. Two of the four surviving cases were examples of post-scarlatinal nephritis.

(C) *Syphilitic Nephritis.*

The case which was first seen at 5½, when re-examined at 9½ years showed no cardiac enlargement and a urea concentration of 3·1. The urine contained a trace of albumen and some cells, but no casts. Œdema had appeared intermittently.

(D) *Interstitial Nephritis.*

Of the two cases of this type one died at the age of 6½, and the other, now aged 8, was too ill to come to hospital for examination.

Conclusions.

Following upon the appearance of nephritis in a child the question naturally arises as to whether an ultimate recovery or some permanent damage to the renal tissue may be expected. The answer to this question would seem to depend largely upon the type of nephritis present in each case. We agree with Hill[2] that the prognosis is best in the acute hæmorrhagic type.

1. Six deaths occurred out of 22 cases of acute parenchymatous type, and one death, from other causes, in the 27 cases of acute hæmorrhagic nephritis.

2. The importance of re-examination at an interval of years is emphasised by the difference in the conclusions which may be based upon an immediate prognosis as compared with the results of later investigations. From a general examination the immediate prognosis seemed good in 13 cases of parenchymatous nephritis and in 26 cases of hæmorrhagic nephritis.

3. After a period of three to five years only five of the parenchymatous cases could be said to have recovered completely, as compared with 12 recoveries in the hæmorrhagic group.

4. Six of the parenchymatous and nine of the hæmorrhagic cases appeared to be in good health, but had albuminuria and abnormal cellular constituents in the urine. The degree of albuminuria and quantity of cells present was definitely less in the hæmorrhagic type than in the parenchymatous cases.

5. Four out of six cases of post-scarlatinal nephritis became chronic. This proportion rather opposes the general opinion that most cases of scarlatinal nephritis end in recovery, but the total figure is too small to be of much value.

6. We emphasise the importance in post-nephritis of the presence of even a very slight trace of albumen when it is associated with an excess of cells in the centrifugalised deposit. This we consider is of definite pathological significance.

The prognosis of syphilitic and interstitial nephritis is well known to be ominous and need not be discussed here. Dr. Still[4] has suggested in the acute nephritis of children that it is " the minority of cases which ever make a complete recovery." In our own series of cases, even in its most benign form, the hæmorrhagic type of nephritis, recovery occurred in less than half the number of cases, namely 44·4%.

We wish to express our gratitude to Dr. G. A. Harrison for his kindness in carrying out the bio-chemical work connected with this paper.

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CURRENT PROBLEMS

IN THE

TUBERCULOSIS OF CHILDHOOD.

Infection, Diathesis, Artificial Pneumothorax, Preventive Inoculation.

BY

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It is a striking fact that tuberculous infection in infancy and childhood has not diminished in proportion to that of the adult. Aschoff,[4] quoting Gottstein, has particularly emphasised this, and he points out that there are still many problems with regard to the pathogenesis of phthisis yet to be solved. A review of certain views on these problems in the light of recent contributions to their study has been undertaken here almost entirely with regard to lung infections.

Routes of Infection.

As far as intra-thoracic tuberculosis in children is concerned the human tubercle bacillus is generally accepted as the important factor, and some authors even go so far as to extend this so as to cover infection elsewhere, largely denying that the bovine bacillus plays the part commonly assigned to it.

A. S. Griffiths[17] collected the results of several investigators on this point and added his own experience as to the type of bacillus isolated from the sputum of phthisical patients, with the result that in 938 cases the bovine bacillus occurred alone in three cases, and a mixed infection of the human and bovine types in another three cases. Calmette[9] has likewise collected the results of 27 investigators, and of 832 cases in only three were bovine bacilli found alone. In 18 cases of primary bronchial gland tuberculosis the human bacillus alone was isolated in 17 cases as reported by Cobbett.[12] Another interesting point in favour of the human origin of the bacillus in pulmonary tuberculosis is the fact that in Japan cow's milk is not employed at all in the feeding of infants, and yet the morbidity and mortality rates of pulmonary tuberculosis are quite as high there as in this country. [Kitasato, quoted by Calmette.[9]] A similar state of affairs is said to exist in Turkey and Greenland.

With regard to the port of entry of the bacillus there are, broadly speaking, three views. Calmette and his school, following von Behring, insist on the importance of the intestinal route. According to this view bacilli are swallowed, pass through the mucous membrane of the intestines

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without leaving any trace, and may either pass up lymphatic channels to the thorax or enter the blood stream and be deposited in the lungs. Calmette's work in which he fed animals on pigmented food and found the pigment in the thoracic glands has, however, been somewhat discredited, and the "intestinal route" has not many supporters at the present time outside France. That infection of the lungs is ærogenous in nature is probably the most widely accepted view. Kuss, H. Albretch, and, later, Ghon, have done a great deal of work on this. Ghon[16] in particular has described the primary lung focus in tuberculosis in children. Out of 184 autopsies carried out by himself he was able in 95% of cases to find a small focus in the lung, usually situated just under the pleura, while the glands draining this area of the lung were enlarged and infected. A small bronchus could usually be traced out to this focus which occurred more frequently in the right than in the left lung, and the changes in the lung were generally more advanced than in the glands; all points in favour of an ærogenous infection. Aschoff[4] has recently called attention to the supreme importance of Ghon's work. While the presence of a primary lung focus is not admitted by many workers, it is generally agreed that the first obvious effect of a tuberculous infection of the lungs is an enlargement of the glands in the neighbourhood of the hilus. This is the "adenopathie-tracheobronchique" of the French and "bronchial-drusentuberkulose" of the German authors for which we have no comprehensive term in English. The third possible route of infection is that in which the tubercle bacillus gains an entry through the lymphatic ring of the pharynx, *via* the tonsils or adenoids, and tracks down through the cervical lymphatic system to the thorax. Cobbett[12] concludes that "tubercle bacilli do occasionally pass through the intact cervical glands when animals are made to swallow very large quantities of these micro-organisms, but that they do so without leaving behind sufficient numbers to produce obvious lesions in these glands has not been established." From experiments on guinea pigs in which a drop of culture of tubercle bacilli placed on the conjunctiva produced a generalised tuberculosis without there being any local lesion Calmette[9] suggests the possibility of the conjunctiva as a port of entry for the tubercle bacillus in human subjects. In an epidemic of influenza among the troops at Lille in 1918 he found that the percentage of those attacked was very much lower among the soldiers who wore glasses than among the troops in general, and this he thinks adds colour to his views as to ocular infection in tuberculosis. The view which lays greatest importance on direct ærogenous infection of the lungs is the most widely accepted, however, and Cobbett[12] summarises the evidence for this under three headings :—

(1) In autopsies on unselected cases lesions are commoner in the bronchial than in the mesenteric or cervical lymphatic glands.

(2) The rarity of the bovine bacillus in pulmonary tuberculosis.

(3) Smaller doses are necessary to produce infection by inhalation than by ingestion.

The way in which the tubercle bacillus is inhaled is also still under discussion. The importance of dust and dried sputum is probably exaggerated. Calmette found it difficult to infect guinea pigs by the intra-tracheal injection of dust contaminated with dried bacilli. On the other hand it was very easy to produce infection by the use of liquid droplets containing the bacilli. The size of the dose is also important. Calmette[9] has a method by which he can estimate the number of bacilli employed, and for a single dose at least fifty bacilli were found to be necessary to infect a guinea pig. On the other hand a small dose repeated over a period will produce the same effect. Four bacilli every day for ten days readily produced infection. It seems therefore that the danger of infection lies entirely in the droplets of sputum containing the bacilli. The recent experiments of Debré and Coste[13] confirming the classical experiments of Flugge, demonstrated this. They exposed guinea pigs in rooms where the examination of pulmonary tuberculosis cases took place and found that the animals were rapidly infected.

The Tuberculous Diathesis.

The question of the tuberculous diathesis is even more controversial than that of infection. This idea would not, however, be gathered from the usual English text books on medicine. Osler discussing the "seed" and the "soil" in tuberculosis deals with the question of predisposition, and quotes the conclusion drawn by Karl Pearson from his statistical studies of the subject that "the diathesis of pulmonary tuberculosis is certainly inherited." Carr in his article in Garrod, Batten and Thursfield's text book on Diseases of Children, writes of the tubercle bacillus that "a diminished resistant power to infection by the microbe may almost certainly be transmitted." Horder, in Price's Text Book of Medicine, states that the existence of the susceptibility to the disease "is one of the cardinal facts of clinical medicine."

There is, however, a considerable body of opinion against these views. Cobbett in England denies that it is proved that a diathesis is inherited, and the modern French school protest strongly against any "inheritance of the soil."

The so-called scrofulous type of child with the *habitus phthisicus* of Hippocrates is probably always already infected. He has the tubercle bacillus shut up in one or more lymphatic gland (Armand-Delille[1]). Calmette states that all such children give a positive reaction to Von Pirquet's test. When tuberculosis occurs in children whose parents or even whose grand-parents have had the disease, the part played by infection and the alleged part played by some inherited counter-disposition cannot be satisfactorily differentiated from a statistical point of view.

Karl Pearson's[18] work went to prove that the ancestors of tuberculous individuals showed a greater incidence of the disease than the ancestors of the same degree of kinship of normal individuals. Many of his results, however, will support the theory of early familial contagion and the question of

husband and wife infection, subsequently brought in to combat the infection theory, is not relevant since in this connection contagion in early infancy is largely ignored. Drolet[14] quotes the Bang method employed in Denmark of separating new born calves from tuberculous cows: the calves so separated remain free from tuberculosis. Such a method has been of recent years applied to the human subject in France, and its results account for the strong views on the question of predisposition held by many French observers.

Bernard[6] points out that the very word predisposition is devoid of meaning. The human race is disposed as a whole to tuberculous infection, and if contagion be eliminated offspring of tuberculous parents are no more liable to develop the disease than any other children. His extensive experience has been that if a child be removed at birth from a tuberculous environment it practically never develops tuberculosis. Thus of 2,500 healthy children removed from tuberculous parents by means of the "Œuvre Grancher," only seven cases of tuberculosis occurred. Of 298 infants as distinct from older children dealt with by the Grancher system also removed in this manner, only 11 deaths occurred from all causes. On the other hand Armand-Delille quoted figures at the Rome Congress on Tuberculosis in 1912 which proved that amongst the children of 175 families where open tuberculosis existed 60% of the children became infected and 40% died from the disease. The contrast between these two sets of figures is overwhelmingly against the diathesis theory. Further, Bernard has shown that amongst 127 children born of actively tuberculous mothers the average birth weight was normal, that after birth at least 62% show a perfectly normal growth curve and that congenital defects and deformities are no more common than among the population at large, all points against any inherited diathesis in his opinion. Out of 124 infants who became tuberculous the infection came from the mother in 95, the father in 20, more distant relatives in three and proved contact at hospital in six cases. Out of 108 infants born of mothers suffering from non-contagious varieties of tuberculosis 30 developed the disease, but contagion in these cases could be traced to the father in 20 instances, to other relatives in three, and to other non-related contacts in six, leaving only one child in which contagion could not be proved. Contagion and not diathesis is the cause of the tuberculosis in these infants. Bernard and Debré[7] consider that there are four main factors which influence the chances of infection in any child :—

(1) The duration of contact with a source of infection.
(2) The degree of contact.
(3) The age at which contamination becomes possible.
(4) The length of survival of the child after separation from the source of infection.

A prolonged contact of, say, six months for an infant which has been suckled from birth by a tuberculous mother is sufficient to make the chance of infection a certainty. This chance is lessened if the father or other member of the household is the contagious source or if the period of contact is only a

matter of weeks or if the child is over a year old when infection becomes possible.

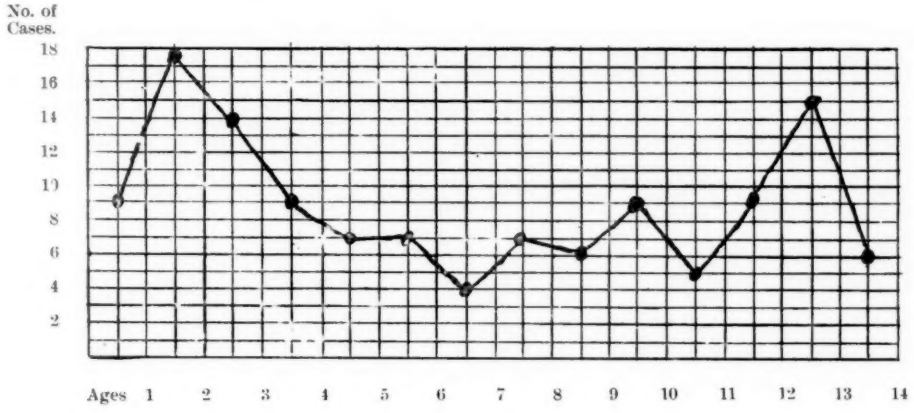
A consideration of these factors in connection with modern views on immunity to tuberculosis, including the question of "allergy" will explain any case of tuberculosis without any reference to a hypothetical diathesis. Any discussion of the principles involved in the immunity problems, however, is impossible in this brief review of the subject.

Artificial Pneumothorax.

The question of artificial pneumothorax in the treatment of pulmonary tuberculosis in children has practically received no attention in this country. The exhaustive report by Burrell and MacNalty[8] for the Medical Research Council a few years ago on artificial pneumothorax makes no mention of its application to children nor does Riviere[21] in his text book on this subject discuss it at all. Both in France and in Germany, on the other hand, this method has obtained a certain amount of popularity. Armand-Delille and others[2] [3] in Paris have employed artificial pneumothorax for a certain number of cases of intra-thoracic tuberculosis. The indications are similar to those in the adult : advancing pulmonary tuberculosis confined to one side, although infection of hilus glands on the opposite side is not considered a contra-indication. Cases of severe hæmoptysis occurring in girls about puberty appear especially amenable to this form of treatment. This author gives a preliminary injection of morphia and employs local anæsthesia. With a Kuss apparatus he injects 25 c. cms. of oxygen at first, after the needle has been introduced in the anterior axiliary line in about the fourth space. If the manometric readings show that the needle is in the pleural cavity 250-300 c. cms. of nitrogen are introduced. Refills take place, after an X-ray photograph at 3-4 day intervals for five injections and then every week or fortnight. He observes that children appear to absorb gas quicker than do adults. In the year 1922 out of 230 cases, 22, all with tubercle bacilli in the sputum, were considered suitable for this form of treatment, about 9% In five of these adhesions prevented collapse. (Even if collapse is incomplete the disease is sometimes arrested.) Of the remaining 17 cases two were allowed to re-expand after 15 months and X-rays showed almost complete absence of any signs of disease. Of the remaining 15, five are in perfect health and the others are all improved. The author points out that to have children with pulmonary tuberculosis alive and well after two years without any cough, with no fever and no tubercle bacilli in the sputum and putting on weight is eminently satisfactory. One case thus treated put on over 20 pounds in the course of a year. In 1923 this treatment was employed for 23 cases out of 262, and of these 16 are "absolutely satisfying." He points out that the course of pulmonary tuberculosis is so rapid in children that most of these cases would have been dead in a few months if pneumothorax treatment had not been instituted. He considers three years necessary to effect a permanent cure.

In Germany, Eliasberg and Cahn,[15] working in Czerny's clinic, have been employing artificial pneumothorax in children. Out of 659 cases of pulmonary tuberculosis, 125 were considered as suitable, and in 111 the operation was successfully carried out. These workers employ air, as the gas introduced and chloroform anæsthesia is occasionally used for the younger patients.

A large number of these cases were under three years of age, 41 of the series, and among the older children girls at puberty seem particularly apt to suffer from active disease and require treatment. The age distribution is interesting, and is shown in the following graph constructed from the authors' figures for 111 cases—



Age Distribution of Pneumothorax Cases.

They consider that $1\frac{1}{2}$ years is necessary for a cure in cases of hilus tuberculosis, and 2 years as a minimum if bacilli have been found in the sputum, although 3-4 years is probably preferable. Of the 111 cases where the treatment was carried out, 50 had bacilli in the sputum and 61 had not, although clinically were undoubted tuberculosis cases. Of the 50 "open" cases—

13 are living	... ...	= 26%
34 are dead	... ...	= 68%
3 are untraceable	... ...	= 6%

Of the 61 "closed" cases—

45 are living	... ...	= 73·8%
9 are dead	... ...	= 14·7%
7 are untraceable	... ...	= 11·4%

Among the 13 living cases in the first group, one has lived two years, five for three years, five for four years, and two for six years. These results are interesting and are set out in some detail here because there appear to be no other published results of any extended trial of this method of treatment which seems to deserve closer attention in this country.

Prophylatic Inoculation.

Balfour and Scott[5] have recently pointed out that the adult mortality rates from tuberculosis are going down and the milk consumption rate is going up, and it is suggested that this may be due to the ingestion of bovine tubercle bacilli in childhood giving rise to some sort of immunity. If then, bovine tuberculosis be eradicated, would we not produce a race of children which would present a virgin soil to infection in later life? But, as these authors point out, the dose of bacilli by this method is always uncertain and undoubtedly for some children is excessive. As Cobbett[12] has expressed it "the harm done by the bovine bacillus is certain, the benefit it confers is problematical." If ingestion of the bovine bacillus by young children does lead to some sort of immunity, it would appear more scientific to give clean milk and attempt to "vaccinate" children against tuberculosis and produce some degree of immunity at any rate for the first few years of life. Such an imitation of the natural process has long been the aim of the French school and Calmette, Guèrin, Weill-Hallé, and others[10] have recently described a special type of tubercle bacillus, which can apparently be used in a living condition without producing any lesions, and which secretes normal tuberculin. This bacillus, known as the "B.C.G." or "Bilié-Calmette-Guèrin," has been obtained by culturing the tubercle bacillus for 13 years by means of 230 successive cultures on a 5% glycerine ox-bile potato medium. After all this time the bacillus has become avirulent and can be recultured on ordinary media. The "vaccination" with this bacillus is only effective and must only be employed in cases where there is no possibility of previous infection and its use is therefore confined to the newly-born. Weill-Hallé and Turpin[22] have employed it in over 300 infants since 1922. They use it in cases where the mother is suffering from active tuberculosis and refuses to be separated from her child. Following Calmette's teaching that the predominant route for the natural infection is intestinal, they give the "B.C.G." by the mouth in doses of one c. grm. for three doses on the third, fifth and seventh, or the fourth, sixth and eighth days after birth, half-an-hour before a feed. Of the first 178 cases treated by this method 15 have died, in no case from tuberculosis. This represents a death rate of 8·4%, while the infantile mortality rate in France in 1921 was 11·6%. The remaining cases have been followed up and they remain well and healthy despite the fact that they are submitted to a continuous infection in the home.

A more recent report on the use of the "B.C.G." by Calmette, Guèrin and others[11] shows that up to June, 1925, altogether 2,070 new born infants had been "vaccinated" in France. Of these cases, scattered in various parts of the country, for many practitioners have applied for the bacillus for their own use, exact details are available in 423, all "vaccinated" at least six months previously. The total deaths from all causes amongst this group amount to 30, a mortality rate of about 7%. Although 137 of these 400 odd cases had been left in contact with some infected person in the family, a tuberculous mother in 86 cases, not one has died from tuberculosis.

Somewhat similar prophylactic measures have been instituted in this country. Pritchard[19] has used injections of various tuberculins for the last 13 years. He usually gives weekly injections to babies for the first six months of life, and he has employed this method in 40 cases, all of which had either a mother or father with active tuberculosis. All these cases are alive and well and the eldest is 12 years of age. Nathan Raw[20] found that rabbits could be protected against infection with the bovine bacillus by means of injections of a vaccine prepared from an attenuated human bacillus. He therefore applied a similar method in children who had one or other parent suffering from active pulmonary tuberculosis. He gave two doses at intervals of two weeks of a vaccine prepared from dead cultures of attenuated bovine bacilli. Altogether 412 children, varying in age from 1½ to 14 years have received this treatment. No untoward reaction nor symptom has followed the use of the vaccine, and so far no child has developed tuberculosis, although as this author points out some time must elapse before the value of this method can be judged. At any rate these three methods of "vaccination" against tuberculosis here described seem to point to a scientific imitation of what some believe to be a natural immunity process which is said to occur in a large percentage of the population and as such deserves extended trial.

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SCIENCE AND THE BRITISH MEDICAL ASSOCIATION.

Readers of the "Archives" will be interested to learn of the new Research Prize on disorders incident to maternity, now inaugurated by the Association. The Prize is being financed by funds which are the generous gift of Mrs. Bishop Harman (London). The Prize for the present will be awarded, usually biennially, firstly and as a general rule, for the best essay or work on any subject within the definition of "disorders incident to maternity," selected by the Council; or secondly, in recognition and encouragement of important work already done or researches instituted and promising good results.

For many years, Laboratory workers have been encouraged by the Association by Scholarships and Grants awarded for the cultivation of research work, and the sum devoted to this end is steadily increasing. By the Middlemore Prize, original work in ophthalmology is recognised, and the Stewart Prize is gained by contributions made to the study of epidemic disease. Of recent years, a subject for Essays has been proposed annually to senior medical students, and Prizes have been allotted to groups of medical schools. A still later action by the Association, with a view to promoting original work of practical value, is the foundation of the Sir Charles Hastings Clinical Prize for encouragement of observation and record in general practice; with it is associated an honorarium of 50 guineas.

Particulars of all the Grants and Prizes awarded by the Association can be obtained on application to the Medical Secretary, British Medical Association House, Tavistock Square, London, W.C. 1.

In the BRITISH MEDICAL JOURNAL, the Association possesses an agency of the highest value for every earnest student of his or her profession. Contributions of recognised scientific and practical merit are received from experts in all departments of professional activity, and clinical notes on diagnosis and treatment also form a feature of every issue. In the JOURNAL are also to be found records of the various professional societies, notices of new books, and an account of modern developments in medicine, surgery and pharmacy.

The following has recently been published by the Association :—PERIODICALS OF MEDICINE AND THE ALLIED SCIENCES IN BRITISH LIBRARIES, by Prof. R. T. Leiper, M.D., D.Sc., F.R.S. The object of this volume is to indicate where much of the periodical literature of Medicine and the allied Sciences may be consulted in London, Cambridge, Edinburgh, Glasgow, Liverpool, Manchester and Oxford. In addition to the more purely Medical Sciences, the work includes the subjects of Agriculture, Anatomy, Anthropology, Bacteriology, Biology, Botany, Chemistry, Ethnology, General Science, Physics, Physiology, Zoology.

At the Annual Meetings of the Association, the discussions in the various Sections attract the leading experts in the profession, and are supplemented by Museum and Hospital demonstrations. On application from a Division or Branch, the Council arranges for a special Lecture to be given to the Division or Branch by an acknowledged expert in any department of medical activity. The meetings of many Divisions and Branches include clinical demonstrations and discussions. Thus, both in his or her immediate locality and at the Annual Meetings, the member of the Association enjoys large educational opportunities, contributing in turn to the common stock of knowledge and education. The Annual Meeting of 1926 is being held at Nottingham, and that of 1927 at Edinburgh.

An Investigation of SCLEREMA NEONATORUM; with Special Reference to the Chemistry of the Subcutaneous Tissues.

(Part II.)

BY

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Chemical Investigation of Subcutaneous Tissues.

A few preliminary determinations only were made by McNee in Cases I. and II. These will be given first. As a result of the experience gained in these two cases, a definite plan of campaign was outlined for the investigation of Cases III. and IV. Case V. recovered spontaneously and no biopsy was made.

A. *Cases I. and II. and Controls.*

The fat was melted out of a mass of subcutaneous fat and dried. The melting point of this separated fat was taken by the capillary method; and the iodine value was determined by Hübl's method.

	Case I.	Control I.	Case II.	Control II.
Age	6 weeks	1 year	12 weeks	9 weeks
M.P. of separated fat, °C. ...	50·5	33·5	38·5	32·5
Iodine value of ditto (Hübl) .	42·1	45·7	52·0	57·5

Control I. died from capillary bronchitis and Control II. from gastro-enteritis.

Cholesterol determinations were made in Case I. and Control I. with the following results (method of Windaus):—

	Case I.	Control I.
Percentage of:—		
Free cholesterol	0·25	Trace
Cholesterol as esters	0·20	0·82
Total cholesterol	0·45	—

B. *Cases III. and IV. and Controls.*

Methods.

The subcutaneous fat removed at autopsy or biopsy from the chest, abdominal wall, arms, or thighs, was cut into small pieces with a scalpel, and then treated in one of two ways. (*a*) The small pieces were spread in a thin layer on a clock glass, and dried to constant weight over calcium chloride in a vacuum desiccator. This usually occupied two or three weeks. (*b*) The small pieces were ground with sand and sufficient anhydrous sodium sulphate to make an "easy flowing" powder. The dry subcutaneous fat, or the powder, was extracted continuously with ether in a Soxhlet apparatus for three or four days (total hours always exceeded 18). Both methods were sometimes used, each on half of the available fat. On comparing the two methods the use of anhydrous sodium sulphate resulted in a slightly better extraction, but the difference was very slight—less than 2%. It was of course essential to employ (*a*) when determining the percentage loss of moisture.

At the end of the three or four days' extraction most of the ether was removed from the ether-soluble portion ("ether extract") on the sand bath, the process being completed in CO_2. Access of air and moisture was prevented by storage in a vacuum desiccator over parafin wax shavings (to remove last trace of ether) and calcium chloride. When constant weight was attained the analyses were started. The residue in the Soxhlet thimble ("ether-extracted residue") was left in the air till the ether evaporated and was then stored similarly.

As many of the following determinations as possible were made upon the "ether extract":—Melting point, acid value, saponification value, iodine value, total cholesterol, and proportion of unsaponifiable matter. The fatty acids were separated, and the following determinations made upon them:—Melting point, neutralisation value (and mean molecular weight) and iodine number. The methods used were the standard ones employed in the determination of fat constants, and need no description beyond the following notes. Melting point: open capillary method; temperature when fat first started to rise in capillary taken as melting point. Iodine value by Wij's method. Total cholesterol by colorimetric method (technique of Bloor, or Myers and Wardell), or using digitonin (Windaus).

Results.

(a) *Examination of the ether extract.*

Our results for cases of sclerema are given in Table VI. and for control cases in Table VII. The melting point values are the mean of two or more determinations. The olein and oleic acid percentages are calculated from the iodine values, on the assumption that they alone were responsible for taking up iodine. This is probably justifiable in the control cases, but not necessarily so in sclerema. In fact there is sufficient cholesterol to increase slightly the iodine value, but only slightly. In Case IV. by means of the

"solid bromide test," traces of highly unsaturated fatty acids were demonstrated, but in such minute amounts as to have no appreciable influence on the iodine value. Bearing in mind the slight increase due to the cholesterol (particularly in the autopsy material from Case III.), even in sclerema it is probably fair to take the iodine value as a measure of the olein or oleic acid content.

TABLE VI.

Results of examination of "ether extract" of subcutaneous fat in sclerema.

Determination.	Case III.		Case IV
	Biopsy material. Age: 5 months.	Autopsy material. Age: 6 months.	Autopsy material. Age: 3 months.
Total: cholesterol %			
by digitonin method ...	1·5 (approx)	6·0	2·1
by colorimetric method ...	2·2	11·0	3·2
Unsaponifiable matter % ...	—	13·6	3·1
M.P. of ether extract, °C. ...	38·5	42·9	47·3
Acid Value	5·4	9·0	5·9
Saponification value	211	206	195
Iodine value	52·3	54·0	45·5
Calculated olein %	60·8	62·7	52·8
Separated fatty acids			
M.P. °C.	—	45·1	49·7
Neutralisation value ...	—	216	206
Mean molecular weight ...	—	260	272
Iodine value	—	48·9	46·7
Calculated oleic acid % ...	—	54·3	51·8

The ether extract from the biopsy material in Case III. only amounted to ½ gm. The results for several of the analyses can therefore only be approximate. The autopsy material from Case III. yielded just over 5 gms., and from Case IV. 7¼ gms. of ether extract. It is considered that the results in these instances are reasonably accurate.

In Case III. three weeks elapsed between biopsy and autopsy. The patient died from intercurrent gastro-enteritis and was very emaciated at death, whereas when the biopsy was performed there was no emaciation. It is possible that the greater concentration of cholesterol (Table VI.) and of calcium (Table IV.) in the autopsy material is largely accounted for by the extreme degree of emaciation that occurred during the three weeks. Fat was absorbed from the subcutaneous depôts during that period, but cholesterol and calcium would be absorbed very much more slowly; in fact it is more than possible that during these three weeks more cholesterol and more calcium may have been laid down.

On ashing the "ether extract" there was no residue, thus excluding the presence of calcium or other inorganic substances.

TABLE VII.

Results of examination of "ether extract" from a series of control cases (autopsy material throughout).

Case No.	a	b	c	d		e	f†		g	h	i
Age	3/12	4/12	8/12	10/12		10/12	1 year		14/12	2 yrs. 10 mths.	40 years
Cause of death ...	Acute gastro-enteritis.	Gastro-enteritis.	Influenzal meningitis.	Abscess of neck and Septicæmia.		Congenital heart disease.	Osteomyelitis. Purulent arthritis. Gastro-enteritis.		Generalised tuberculosis.	Osteomyelitis.	Placenta prævia.
				Gluteal region.	Chest and abdominal wall.						
Total cholesterol % by colorimetric method.	—	—	—	0·18	0·19	—	(x) —	(y) —	—	—	0·26
M.P. of ether extract °C	36·8-37·8	30·5	27·9	28·4	29·4	32·7	22·0	26·9	29·0	21·5	27·3
Acid value	2·0	1·7	1·2	1·1	0·6	2·7	0·4	0·9	0·9	Nil.	Nil.
Saponification value ...	206	203·6	199·7	190·3	203	203·3	197·7	201·8	198·3	199·4	199·0
Iodine value	53·8	56·9	60·6	68·7	56·6	57·4	53·3(?)	58·4	61·0	67·5	65·0
Calculated olein % ...	62·5	66·1	70·4	79·7	65·7	66·8	61·9(?)	67·8	70·8	78·3	75·5
Separated fatty acids *											
M.P. °C	—	38·6	36·1	—	—	39·9	34·8	37·8	35·8	34·0	33·5
Neutralisation value	—	214·5	209·6	—	—	209·7	209·0	209·2	206·5	206·6	207·0
Mean molecular wt.	—	261·8	267·7	—	—	267·5	268·8	268·1	271·8	271·5	271·0
Iodine value ...	—	59·6	62·4	—	—	59·8	57·6	61·1	62·9	70·3	65·7
Calculated oleic acid %	—	66·2	69·3	—	—	66·5	64·0	67·9	69·9	78·1	73·0

* The separated fatty acids include the unsaponifiable matter.

† 2 portions of fat (x) and (y) both from chest and abdominal wall, each extracted and analysed separately.

(b) *Examination of the "ether-extracted residue."*

Reference to the estimations of calcium and of total phosphorus has already been made (Tables IV. and V.).

C. *Special experiments.*

(1) The effect of added cholesterol on the melting point of an ether extract of subcutaneous fat:—

	M.P °C.
Control fat (non-sclerematous)	28·4
plus 2% cholesterol	28·5

The addition of 2% cholesterol had no effect.

(2) The effect of added palmitin on the melting point of an ether extract of subcutaneous fat:—

	Added palmitin, as per cent. of resultant mixture.	Average M.P.°C.	Elevation of M.P.°C.
Control fat (non-sclerematous) ...	Nil	27·0	—
„ „ plus pure palmitin ...	3·0	35·9	8·9
„ „ „ „ ...	7·1	44·0	17·0
„ „ „ „ ...	28·4	53·7	26·7

The addition of tripalmitin had a marked effect on the melting point of the resultant mixture. Or to put this in another way the artificial reduction of the percentage of olein greatly increased the melting point.

Literature.

It is convenient to give a summary of the literature on the chemistry of the subcutaneous fat under two headings: (a) Non-sclerematous patients, (b) Cases of sclerema.

(a) *Non-sclerematous patients.*

Langer[15] noted the difference between the subcutaneous fat of infants and that of adults as regards melting point and consistency. He found that infants' fat yielded 31% solid-fatty acids, whereas the figure for adults' fat was less than 10%. He stated that a large part of the fat in the fat-cells of the infant was solid and opaque above body temperature.

Lebedeff[17] stated that Chevreul found that the melting point of human subcutaneous fat was 20-22°C. Lebedeff analysed the subcutaneous fat from a man who died from apoplexy. He separated the liquid fatty acids by the lead-salt-ether method, and was careful to avoid oxidation by working in a current of CO_2. He found 80 and 78·6% oleic acid respectively in duplicate analyses.

Raudnitz [28] determined the melting point of the subcutaneous fat from an infant of 2 days and from a child of 2 years. In the former he found a range of 42·3 to 44·6°C. (fat of back 43·8, of chest 44·6, and of gluteal region 42·3°C.), and in the latter a range of 28·7 to 30·2°C.

Mitchell [22] who is often quoted in German literature, worked with perirenal and not with subcutaneous fat.

Knöpfelmacher[14] found that the iodine value of the subcutaneous fat of a new-born child was lower than that of an adult. On the basis of analyses in seven cases (Table VIII.) he suggested that the olein percentage of infant's fat increases until at the age of about 12 months it reaches the "adult" level. He made the interesting observation (which so far as I know has never been confirmed) that the heel fat (and palmar fat) was peculiar in that it, in contrast with the fat from the chest, back and thigh, at birth already contained the full complement of olein.

TABLE VIII.

Knöpfelmacher's results in non-scleromatous patients.

Case No.	Age.	Cause of death.	Neutral fat.			Separated fatty acids.			Calculated oleic acid per cent.	Solid fatty acids (by difference.)
			M.P. °C.	F.P. °C.	Iodine value.	M.P. °C.	F.P. °C.	Mean iodine value.		
1	New-born	—	43	38	39·05	48 (Heel fat :	44	40·08 60·6	49·49 67·28)	55·41
2	7 weeks	Lues hereditaria	37	30	—	43	39	42·84	47·56	52·44
3	7 ,,	,, ...	34	28	—	44	37·5	50·35	55·9	41·1
4	6 months	Diphtheria ...	31	25	—	41·5	37	50·98	56·6	43·4
5	10½ ,,	,, ...	—	—	—	39	35	55·53	61·09	38·91
6	12 ,,	Tuberculous meningitis	—	—	—	37 (Heel fat :	33·5	63·75 61·8	70·77 68·56)	29·23
7	17 ,,	Purpura haemorrhagica	—	—	59·25	37	32	64·53	71·64	28·36

Thiemich [34] determined the iodine value of the fatty acids separated from the subcutaneous fat of 17 non-sclerematous infants of different ages. He confirmed the fact that very young infants' fat is poorer in olein than that of adults. He was, however, unable to confirm Knöpfelmacher's suggestion that there was a regular increase in the iodine value from birth till the age of 12 months.

Siegert[31] likewise determined the iodine values of the separated fatty acids in 26 non-sclerematous infants. He combined his own results with those of Knöpfelmacher and of Thiemich. Unfortunately, however, he included the sclerema cases in his table. In Table IX. these findings are reproduced, but with omission of the sclerema results.

TABLE IX.

Non-sclerematous cases of Knöpfelmacher, Thiemich and Siegert.
Iodine value of separated fatty acids according to age.

Age.	No. of cases.*	IODINE VALUE.		
		Lowest.	Highest.	Average.
Premature. 8 months ...	2	46·8	49·4	48·1
New-born	12	38·8	49·2	43·3
1 day to 1 month	5	38·1	48 7	43·9
1 month to 2 months ...	5	38·45	51·4	46·7
2 months „ 3 „ ...	2	41·5	53·5	47·5
3 „ „ 4 „ ...	6	41·4	58·9	53·2
4 „ „ 5 „ ...	3	42·3	47·8	45·5
5 „ „ 6 „ ...	4	47·0	51·47	49·9
6 „ „ 8 „ ...	4	46·1	52·9	48·9
8 „ „ 10 „ ...	3	51·7	61·6	57·0
10 „ „ 12 „ ...	3	55·5	63·7	60·1

* Total number of cases, 49.

Siegert concluded that it could be definitely accepted that the fat of young infants contains less olein than that of adults He pointed out that, allowing for the difficulties of analysis and the fact that the number of cases tested was small, the results for the first eight months of life were fairly uniform. Between the eighth and twelfth months the iodine value rapidly reached the adult level of about 65. He suggested that the explanation

might lie in the change from a purely milk diet to a mixed diet which usually occurs at this period of infancy. In Table X. are included the results published since Siegert's paper. It is felt that this larger group bears out his contention.

TABLE X.

Non-scleremátous cases of Knöpfelmacher, Thiemich, Siegert, Jæckle, Bardisian, Finkelstein & Sommerfeld, and Lasch.

Iodine value of separated fatty acids according to age

Age,	No. of cases.	IODINE VALUE.		
		Lowest.	Highest.	Average.
Premature. 8 months ...	2	46·8	49·4	48·1
New-born	16	36·9	49·2	42·2
1 day to 1 month	7	38·1	60·7	47·1
1 month to 2 months ...	5	38·45	51·4	46·7
2 months „ 3 „ ...	6	41·5	58·7	50·1
3 „ „ 4 „ ...	9	41·4	75·5	57·4
4 „ „ 5 „ ...	4	40·6	47·8	44·3
5 „ „ 6 „ ...	6	47·0	53·3	50·9
6 „ „ 8 „ ...	7	46·1	56·2	49·6
8 „ „ 10 „ ...	3	51·7	61·6	57·0
10 „ „ 12 „ ...	4	55·5	63·9	61·0
Adult	—	—	—	65·0

NOTE.—Total number of cases, 69. In the majority of instances the determination of the iodine value was made directly on the separated fatty acids In a minority of cases the determination was made on the neutral fat (glycerides). In these latter cases the approximate corresponding value for the separated fatty acids has been calculated, and these calculated figures have been included in the above table. In the case of Lasch's results, his findings for the subcutaneous fat from the thigh or, if no analysis is given for the thigh, the results for the fat from the cheek have been taken. Case No. 8 is omitted since Lasch found an iodine value of only 22·6, whereas that of the abdominal fat of the same patient was 54·0.

Jæckle[12] questioned the absolute accuracy of the methods of previous workers, but accepted the general conclusions of Siegert. He recorded his own analyses in two infants and seven adults. He found that human fat was composed essentially of the glycerides of oleic, palmitic and stearic acids, with but a mere trace of lower acids. He noted the influence of the state of nutrition on the results of analysis, and stated that the fat of man and

of other higher animals was of practically the same composition. Likewise he found the composition of lipoma fat to be very similar to that of subcutaneous fat.

Bardisian[3] compared the composition of fat from three sources (subcutaneous, mesenteric and perirenal) in each of five children to see if there were any differences. The idea was suggested to him in view of the fact that lard from different sources varies in composition. He did find slight differences, but one is here concerned solely with his results for subcutaneous fat. Only one of his patients was under 1 year of age, and in this case only the iodine value of the neutral fat was low (Age 3 months: iodine value 50·3. Ages 19 months to 5½ years: iodine value 60·1 to 63·2).

Finkelstein and Sommerfeld[8] summarised the previous work of German investigators and added their own results in two non-sclerematous patients.

Lasch[16] studied the composition of the fat from different parts of the body particularly in regard to the iodine value. From analyses in 16 cases of ages between birth and 10½ months, he concluded that there was no significant difference in the iodine values of fat taken respectively from the cheek, sucking pad, thigh and abdomen.

The values for the fat constants of the subcutaneous fat of children and of adults recorded in the literature, may conveniently be summarised in the following notes:—

Neutral Fats (glycerides).

(i.) Melting point.

There is a general agreement that the melting point of the fat of newborn and very young infants is higher than that of adults, but the recorded figures do not decrease regularly with increase in age. Highest figure recorded 44·6°C., in an infant 2 days' old (Raudnitz). Figures for the first six months of life vary between 44·6 and 23°C. Thereafter the melting point usually lies between 30 and 19°C.

(ii.) Solidification point.

Again there is a general agreement as to the difference between infants and adults, with irregular levels as for the melting point. Highest figure (Knöpfelmacher) at birth 38°C. Most writers regard the solidification point as too indefinite to be of any value.

(iii.) Iodine value.

From birth to the end of the eighth month the iodine value varies between 35 and 55, though occasionally higher figures have been recorded. From the end of the eighth month to about the twelfth month the iodine value rapidly rises to the adult level. The value in adults most commonly lies between 57 and 65, though figures as high as 73 have been recorded.

(iv.) Saponification value.

There are very few recorded analyses in children. Jæckle[12] found 204·4 in each of his two infants under 1 month, and figures varying from 193·3 to 199·9 in his seven adult patients. Bardisian's[3] figures ranged from 212 to

228 in his five children of 3 months to 5½ years. Bardisian's results are higher than those given by most authorities. An average figure for adults may be taken as 195 with a range commonly between 193 and 200.

(v.) Acid value.

The amount of free acid in human subcutaneous fat usually amounts to a mere trace. The acid value is generally less than two.

(vi.) Cholesterol.

Unna and Golodetz[35] found that the subcutaneous fat contained the following:—

Free cholesterol	0·14%
Cholesterol as esters	0·04%
Total cholesterol	0·18%

Separated fatty acids.

(i.) Melting point.

The melting point of the separated fatty acids runs parallel with, and at a slightly higher level than, the melting point of the corresponding neutral fats. The remarks made in connection with the latter apply equally to the former. The highest recorded melting point of subcutaneous fatty acids is 48°C. (Knöpfelmacher) in a new-born infant.

(ii.) Solidification point.

This lies at a slightly higher level than that of the corresponding neutral fat. The highest recorded figure is 44°C. (Knöpfelmacher) in a new-born infant.

(iii.) Iodine value.

This runs parallel with, and at a slightly higher level than, that of the corresponding neutral fat:—

Birth to end of eighth month	36 to 58
Ninth month to one year	50 to 65
Average adult level	65
Usual range in adults	62 to 70

(iv.) Neutralisation value and mean molecular weight.

No data appear to have been recorded in children or in adults.

All the available literature on analyses of the subcutaneous fat in children has been reviewed. For further accounts of similar analyses in adults, the reader is referred to the papers of Partheil and Ferié[26] and of Unna and Golodetz[35] and to the works of Abderhalden[1] and of Lewkowitsch and Warburton[18]. On the whole, very little work on human subcutaneous fat has been reported.

(b) *Cases of Sclerema.*

In the literature there are 18 cases of sclerema neonatorum in which chemical analyses are recorded. These are summarised in Table XI. It will be seen at a glance how meagre are the chemical data on which hypotheses as to the causation of sclerema have been based. Apart from estimations of the iodine values and of the oleic acid percentages, very little has been done.

TABLE XI.

Summary from literature of chemical analyses of subcutaneous fat in sclerema neonatorum (sclerema adiposum).

Authority.	No. of Case.	Age.	Neutral Fats (Glycerides)						Separated Fatty Acids				
			M.P. °C.	F.P. °C.	Iodine Value.	Calcd. Olein %	Acid Value.	Saponification No.	M.P. °C.	F.P. °C.	Iodine Value.	Calcd. Oleic Acid %	Estimated Oleic Acid (Lead Salt Method)
Knöpfelmacher ...	1	25 days ...	44	36	—	—	—	—	48	44	38·53	42·8	—
	2	3 weeks ...	43	36	—	—	—	—	48	42 (Heel fat:	39·7 60·73	44·1 67·5)	—
Thiemich	3	1½ months ...	—	—	—	—	—	—	—	—	48·1	53·4	—
	4	3½ months ...	—	—	—	—	—	—	—	—	53·2	59·1	—
	5	3½ months ...	—	—	—	—	—	—	—	—	53·3	59·2	—
Siegert	6	Prem. 8/12 ...	—	—	—	—	—	—	—	—	35·6	39·6	—
	7	,, ,, ...	—	—	—	—	—	—	—	—	37·7	41·9	—
Miura	8	—	—	—	—	—	—	—	—	—	—	—	40·32* (control new-born 41·31)
Sarvonat	9	—	23	—	43	49·9	—	—	—	—	—	—	56·0*
Carpenter & Neave (6)	10	6 weeks ...	—	—	—	—	—	205	—	—	—	—	—
Bayer	11	Twin: 9 days	52	Inconstant	Inconstant	—	—	—	—	—	—	—	23·4
	12	,, 15 days (Control twin	70 35)	,,	,,	—	—	—	—	—	—	—	24·0 (control twin 62·0)
Smith	13	20 days ...	37·5	—	44–48	51–56	163	190	—	—	—	—	—
Finkelstein u. ...	14	6 days	—	—	55	63·8	—	—	—	—	—	—	60
Sommerfeld	15	4 weeks ...	—	—	53	61·6	—	—	—	—	—	—	64
	16	6 weeks ...	—	—	60	69·7	—	—	—	—	—	—	70
	17	3 months ...	—	—	58	67·4	—	—	—	—	—	—	68
	18	10 months ...	—	—	61	70·8	—	—	—	—	—	—	73

* Method of Estimation of Oleic Acid not known because papers not available. These figures are quoted from Smith's paper.

Langer[15] suggested that in diseases of infants a preferential oxidation of olein might occur. The resulting increase in palmitin and stearin might easily lead to a hardening of the subcutaneous fat even in the presence of hyperpyrexia. When there was a fall in body temperature the fats might readily solidify.

Knöpfelmacher[14] believed that sclerema was due to a combination of three factors, (a) loss of fluidity of the subcutaneous fat, (b) lowering of body temperature, and (c) the high level of the solidification point of the fat of infants. He considered that sclerema was seldom possible after the second, and never possible after the sixth month. Subsequent clinical observations have proved this latter statement to be incorrect. Knöpfelmacher suggested that the freedom of the soles and palms from sclerema might be accounted for by his observation that the heel fat contained its full complement of olein already at birth. (*See* Tables VIII. and XI.)

The analyses of Thiemich[34] included observations on the iodine value of the separated fatty acids in three cases of sclerema. Thiemich found no significant differences between the iodine values of scleremato us infants and those of non-scleremato us infants of corresponding ages.

Siegert[31] included two cases of sclerema in premature infants in his extensive investigation of the iodine value of the separated fatty acids of the subcutaneous fat. He pointed out that the diminished olein hypothesis of sclerema could not hold, in view of Thiemich's observations on two cases of sclerema whose ages were 3½ months, and whose iodine values were 53·3 and 53·2 respectively (Table XI.). He further noted that the iodine value was often below 50 in patients who did not develop sclerema. Also in spite of a great loss of fluid, a low body temperature, and a low iodine value in many new-born and very young infants, the development of sclerema was exceptional. He further excluded the state of nutrition as the cause of low iodine values. Some of his very emaciated infants had just as high iodine values as some of his obese infants. Also he pointed out that it was a mere assumption that olein was more readily oxidised than stearin and palmitin in cases of rapid emaciation.

Miura[23] " concluded that the fat of scleremic infants did not differ materially from the fat of normal infants of the same age."

Sarvonat[29] " concluded that neither the body temperature nor the oleic acid content would explain the hardening of the tissues."

Bayer[4] in a lecture maintained that sclerema was due to a pathological reduction of the content of oleic acid. He gave only a brief summary of his own work and no details of the methods he used. He found the melting point of the subcutaneous fat in sclerema very much raised (Table XI.). In fact one of his figures (M.P. 70°C.) is unique—so much so that one is tempted to question its accuracy. His figures for the oleic acid content in sclerema are very low in comparison with his control cases.

Smith[32] reviewed most of the previous literature, and added his own analyses in one case of sclerema. He made his determinations on the "normal" and "abnormal" fat from his case. It would seem to be impossible thus to separate with the unaided eye sclerema fat into two parts. A portion which is normal macroscopically often shows the typical changes in an earlier stage microscopically (compare remarks of Dr. McNee in histological report on Case I.). Smith did not support the diminished oleic acid hypothesis, and suggested tentatively that the changes in sclerema were similar to those in fat necrosis. Smith's acid values are extraordinarily high —so high in fact that one suspects that post-mortem hydrolysis took place.

Finkelstein and Sommerfeld[8] summarised previous findings in tables, and added their own results in five cases of sclerema. They discussed previous hypotheses and concluded that most of these were negatived on clinical grounds. They suggested that sclerema was due to some change in the colloids of the subcutaneous tissues.

General Review of Results.

Any hypothesis as to the pathology of sclerema neonatorum must be such as to embrace the following facts which have been found to be characteristic of the condition:—

(1) Solid consistency of fat during life.

(2) Histological picture of chronic inflammation with giant-cell formation and calcification.

(3) Presence of anisotropic crystals in the frozen sections.

(4) X-ray findings.

(5) Excess of calcium and of phosphorus in the subcutaneous fat.

(6) Excess of cholesterol in the subcutaneous fat.

(7) Raised melting point of separated fat and of ether extracts of subcutaneous fat.

(8) Iodine value and saponification value of subcutaneous fat within normal limits.

Previous work, and our own findings in the light of the above observations, may now be discussed.

The Solid Consistency of the Subcutaneous Fat.

It was suggested by Langer in 1881 that a fall in the surface temperature of the body in sclerema allowed the fats to come out of solution. Such a fall in body temperature might, he thought, be due to improper clothing or to exposure to cold air or water. This hypothesis scarcely requires discussion. In the first place a fall of more than a very few degrees in body temperature is incompatible with life. In the second place the fat of dead non-sclerematous infants (temperature that of the surroundings) does not have as solid a consistency as that of living sclerematous patients (temperature that of the body). In Langer's cases, which were of the severe type, the body temperature was subnormal. In our cases, which were of a milder type,

the body temperature was normal or raised, and yet the subcutaneous fat was of a solid consistency in patches. A number of previous investigators have discarded this hypothesis as untenable.

Practically the only other hypothesis that has been advanced was founded on the observation that the melting point of the subcutaneous fat in sclerema was higher than that of non-sclerematous infants of corresponding ages (Knöpfelmacher, Bayer). The next point for discussion therefore is the cause of this rise in the melting point of the subcutaneous fat.

In the present series of cases of sclerema the melting point of the fat was found to be raised slightly, and this, together with the presence of crystals, an excess of fibrous tissue, and the patches of calcification, can be regarded as the cause of the solid consistency of the fat during life.

The Cause of the Raised Melting Point of the Subcutaneous Fat in Sclerema.

It was definitely shown by the work of Knöpfelmacher, Thiemich and Siegert, that the subcutaneous fat of normal young infants contains less olein than that of adults. Subsequent investigations and our own analyses (Table VII.) are in agreement with this. Is the slightly raised melting point in sclerema due to a further diminution in the content of olein? The work of Langer, Knöpfelmacher and Bayer is in favour of this hypothesis, the work of Thiemich, Siegert, Miura, Sarvonat, Smith, and Finkelstein and Sommerfeld is against it.

In our own work no *significant* differences between the iodine values of sclerematous and non-sclerematous fat respectively have been found (compare Table VI. with Table VII.), but it does not follow that this necessarily disproves the diminished olein hypothesis. It is well known that the melting point of fat mixtures may be altered considerably by relatively slight variations in the composition of the mixed fats. The experiment on the addition of palmitin to non-sclerematous ether extract illustrates this forcibly. One would hesitate before attaching any significance to variations of 3% in estimations of the iodine value, yet variations of the order of 3% in the olein content might influence very appreciably the melting point. In other words an estimation of the iodine value is a relatively crude measure of the olein content. In view of the absence of any other more likely hypothesis, one is inclined to agree that the raised melting point in sclerema may be due to an increase in the proportion of fats of higher melting point.

When we started this investigation[37] it was thought that the anisotropic crystals in the frozen sections would turn out to be cholesteryl esters, and that possibly an increase in the cholesterol content of sclerema fat might explain the raised melting point. The addition of 2% of cholesterol to non-sclerematous ether extract, however, did not alter the melting point.

The Nature of the Anisotropic Crystals.

On reference to the literature, a number of statements are found as to the presence of crystals in the fat both of sclerema and of normal infants,

Thus Knöpfelmacher[14] states that each globule of normal infant's fat contains numerous "fatty acid" crystals, and Harris, in the discussion following Lieberthal's paper[19], refers to a case of sclerema in which "he opened a couple of areas and pressed out a mass of sebaceous-looking material containing lobules of oil which, under the microscope, was found composed of needle-shaped crystals."

A careful search of the literature has been made, but no serious attempts to determine the nature of the crystals seen in body fats has been discovered. My own findings will be discussed.

It has been shown in the section on the histochemical examination of crystals in the subcutaneous fat, that the subcutaneous fat of normal (non-sclerematous) children contains an abundance of anisotropic acicular crystals. Presumably these "normal" crystals are either stearin or palmitin. Are the sclerema crystals also composed of neutral fats?

The solubilities of the sclerema crystals exclude the possibility of their being soaps or urates. The low acid values of the ether extracts makes it unlikely that the abundant sclerema crystals are free fatty acids, though it is to be noted that the acid values of sclerematous fat are slightly higher than those of non-sclerematous fat. The behaviour of the sclerema crystals towards alkaline alcohol however (*see* Table I. and contrast with experiments on palmitic acid crystals) rules out the possibility of their being free fatty acids.

It is unlikely that the sclerema crystals are composed of cholesteryl esters for the following reasons:—(a) Microchemical tests for cholesterol were negative; (b) on carefully warming the crystals under the polarising microscope, and then cooling, no evidence of the formation of fluid crystals was ever noted; (c) the melting point of the sclerema crystals was lower than the melting point of true cholesteryl esters (*e.g.*, as seen in frozen sections of cutaneous xanthoma); (d) had the sclerema crystals been cholesterol compounds, one would have expected, owing to the large quantity of crystals seen in the sections and ether extracts, that the cholesterol content of the ether extracts would have been much higher than that actually found.

The solubility of the sclerema crystals in acetone makes it unlikely that they are phosphatides or cerebrosides. The presence of these latter compounds is also negatived by the absence of liquid crystal formation ("Maltese crosses"). Also the extract, made by means of ether, in which solvent the sclerema crystals are soluble, when ashed, left no residue.

It is concluded therefore that the sclerema crystals are in all probability neutral fats—either palmitin or stearin or both, or the glycerides of higher fatty acids. The observed properties (Table I.) fit in well with this hypothesis, and the experiments with palmitin provide no evidence against it.

If this work be confirmed, it should in future be made clear that the behaviour of *crystals* in polarised light is *not* a sure method of differentiating neutral fats ("true fats") from lipoids.

Do the Sclerema Crystals Exist as such during Life?

They probably do for the following reasons:—

(*a*) The melting point of the sclerema crystals as seen in frozen sections exceeds 40°C.

(*b*) The clefts seen in the paraffin sections and the arrangement of giant cells around some of these clefts is strongly suggestive of the existence of crystals *in vivo*.

(*c*) Masses of crystals were observed as little white lumps at the moment of aspiration of the fluid from the cysts in Case III.

Hypothesis as to the Pathology of Sclerema.

From a consideration of the evidence presented in this paper the following hypothesis is submitted tentatively.

Sclerema neonatorum is due to a peculiar inflammatory change which occurs in the subcutaneous tissues of infants, the cause of the inflammation being unknown. The condition is closely allied to "fat necrosis."

The histological examination of our cases presents undoubted evidence of a chronic inflammatory reaction. The question is whether this inflammation is of "chemical" or of "bacterial" or of some other origin. At first, owing to the presence of crystals in the frozen sections, and the clefts in the paraffin sections, one was inclined to look to some disturbance of the chemical metabolism of fat as the primary event, and to regard the inflammatory reaction as secondary to local irritation by the crystals. In view, however, of finding so little alteration in the chemical composition of the fat and in view of the conclusion that the sclerema crystals are composed of neutral fats, one is now more inclined to the view that the inflammatory reaction was primary and the chemical changes secondary to the inflammation. At the present moment any interpretation must remain a matter of personal opinion. At a later date it is hoped that the question may be submitted to bacteriological investigation and to experimental enquiry.

It is, however, necessary to discuss whether the above hypothesis could embrace all the observed facts.

If a primary inflammation of the subcutaneous fat be assumed there is no difficulty in interpreting the rest of the findings. Here and there the inflammation has been severe enough to lead to death of tissue. This in accordance with the generally accepted pathological "law" would be followed by deposition of cholesterol and calcification, thus explaining the chemical findings of an excess of cholesterol and calcium. The calcification would account for the X-ray findings. It is not unreasonable to assume that the mobilisation of fat from the subcutaneous depôts would be affected by the presence of a chronic inflammation, thus possibly leading to a slight preferential absorption of the fats of lower melting point. As a result there would be a tendency for the higher melting point fats to crystallise out.

There would seem to be no serious objection to supposing that the giant cells appear in response to irritation by the neutral fat crystals. As has already been noted, a preferential absorption of olein might easily account for the raised melting point, and yet be so slight as not materially to alter the fat constants. The raised melting point of the fat, with the crystalline deposits, possibly in conjunction with the products of inflammation and repair (fibrous tissue, cholesterol deposits and calcification) would readily account for the solid consistency of the fat observed during life.

In adopting tentatively the above as a working hypothesis of the pathology of sclerema one has no doubt been influenced by the reports in the literature. Thus Fabyan[7] describes a case of "Disseminated Subcutaneous Fat Necrosis occurring in an Infant without other lesions." A study of his report leads to the conclusion that his case was one of sclerema neonatorum. Smith[32] refers to Fabyan's case also and suggests, indirectly at any rate, that it was an example of sclerema. Smith concludes that in his own case of sclerema the changes observed were similar to those of fat necrosis. Wells[36] in his section on "Fat Necrosis" also refers to Fabyan's case and notes that it may have been one of "scleroderma."

Summary.

(1) Five cases of sclerema neonatorum (adiposum) are reported, with post-mortem and histological findings in four. The fifth recovered. In two cases there were cysts in the subcutaneous fat.

(2) Histologically in the four cases the subcutaneous fat showed evidence of chronic inflammation and repair, with giant-cell formation. In each there were abundant anisotropic crystals in the fat and lying free.

(3) From histochemical studies it is concluded that the anisotropic crystals consist of neutral fats (glycerides).

(4) The X-rays revealed opaque deposits. Calcification is indicated histologically, and chemically there is an excess of calcium and of phosphorus in the subcutaneous tissue.

(5) The chemistry of the subcutaneous fat has been studied in four cases —extensively in two. The melting point was raised slightly, and there was an increase in the total cholesterol, but the iodine and saponification values were similar to control cases of corresponding ages.

(6) The literature of the chemistry of the subcutaneous fat in sclerema and in non-scleromatous cases is reviewed.

(7) The pathogenesis of sclerema is discussed, and the view that sclerema is a primary inflammation of the subcutaneous tissues of unknown cause is upheld.

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NEPHRITIS IN CHILDHOOD

BY

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The investigations upon which this paper is based were undertaken primarily to examine the practical value of the so-called "renal efficiency tests" in children. Cases of kidney disease admitted to one of the medical wards of the Royal Liverpool Children's Hospital were systematically examined, and the results have been analysed. This has necessitated a general survey of kidney diseases, and of the special peculiarities of these diseases in children. So far as possible, the pathological and clinical aspects have been correlated in the classification adopted; and an attempt has been made to emphasise the necessity of taking a broad general view of each case studied.

The paper is sub-divided under the following headings:—

1. Classification of nephropathies.
2. Methods of investigation.
3. Description of cases studied.
    (A) Acute glomerulo-nephritis.
    (B) Chronic glomerulo-nephritis.
    (C) Diffuse tubular nephritis.
4. Pathological findings in diffuse tubular nephritis.
5. Treatment.
6. Summary and conclusions.
7. Bibliographical references.

1. Classification of Nephropathies.

It must be admitted that there is at the present time no satisfactory classification of kidney diseases. Of the many schemes which have been suggested (Heubner[12], Newburgh[27], Schwartz and Kohn[28], and Tripputi[31], etc.), one of the best-known is that of Volhard and Fahr[32], which is here reproduced in abridged form (Table A). This classification has a pathological

TABLE A.

Classification 1.

(Modified from Volhard and Fahr.)

A. *Nephrosis.* Müller, 1905. (No increase of B.P.)

B. *Nephritis.*
    1. Diffuse glomerulo-nephritis. (Increase of B.P.)
    2. Focal nephritis. (No increase of B.P.)

C. *Renal Sclerosis.*

rather than a clinical foundation, and it marshals cases of kidney disease under three main heads—degenerative, inflammatory and sclerotic; or, in other words, nephrosis, nephritis, and renal sclerosis.

(A) *Nephrosis* is comparatively a rare condition in which the cells lining the kidney tubules show degenerative changes, without any evidence of inflammation elsewhere in the kidney (*e.g.*, glomerular changes). The various types of degeneration which may be found are stated by Munk[25] to be as follows:—Cloudy swelling or albuminous, fatty, lipoid (*cf.* myelin kidney of McNee[19]), necrotic, hyaline, amyloid, and possibly glycogen-degeneration in diabetes mellitus.

Poisoning with heavy metals and intestinal intoxication may be mentioned as possible causes of nephrosis.

The studies of Epstein[9] and of Major and Helwig[20] seem to show that other characteristic features of nephrosis include hypercholesterinæmia, a low metabolic rate and a great increase of serum-albumin as compared with serum-globulin.

(B) *Nephritis* is comparatively a common disease in which the kidneys show signs of inflammatory response; for instance, hyperæmia and swelling of the tufts, outpouring of exudate and of cells into the capsules of Bowman, leucocytic and lymphocytic infiltration of the interstitial tissue, and degenerative changes in the cells lining the kidney tubules.

(C) *Renal sclerosis* is a common lesion in adults, but is very rare in children. I shall not consider it in this paper.

Clinically, one of the most important features of nephrosis is extensive and persistent œdema; whereas in nephritis, œdema is variable in degree and frequently is not a prominent feature.

Volhard and Fahr[32] divided their nephritic cases into two groups, diffuse glomerulo-nephritis and focal nephritis, the difference between them being mainly clinical and concerning the blood pressure. They recognised, furthermore, that focal nephritis may be (1) glomerular, for instance in endocarditis, especially if due to the streptococcus viridans; (2) embolic; or (3) of the septic or acute interstitial type (Councilman), seen occasionally in diphtheria and also after scarlet fever where the throat infection has been very severe.

If the distinction which differentiates "nephrosis" from the better-known and older term "parenchymatous or tubular nephritis" is not properly appreciated, the modified classification of Volhard and Fahr appears to be no advance upon the former terminology. A certain laxity in adhering to the terms of definition, together with the clinical fact that examples of "parenchymatous or tubular nephritis" frequently bear a close resemblance to cases of nephrosis, has led several writers to describe as "nephrosis" cases in which there was evidence of inflammation of the kidneys. My own investigations, though comparatively few in number, demonstrate the applicability to childhood of Volhard and Fahr's statement that nephrosis is a rare condition; and in order properly to record the pathological lesion

which exists in a majority of "large white children," I have suggested a classification (Table B) which is in essence a reversion to the older scheme, but provides also a place for examples of true nephrosis.

TABLE B.

CLASSIFICATION 2.

A. *Nephrosis.* (Some cases of parenchymatous nephritis.)

B. *Nephritis.*

1. Glomerulo-nephritis { General; Local or { Focal nephritis of Volhard and Fahr. / Pædonephritis of Heubner.
2. Diffuse tubular nephritis. (Most cases of parenchymatous or tubular nephritis.)
3. Focal nephritis.
   - (*a*) Acute interstitial nephritis.
   - (*b*) Acute and subacute embolic nephritis.

C. *Renal Sclerosis.*

It is a truism to state that when a child's kidneys become inflamed, it is rare to find on histological examination that any one of the component structures of the kidney has escaped: there are few examples of nephritis which do not show *diffuse* nephritis.

I have employed the word "diffuse" to emphasise one special and important feature found in the kidneys of "large white children," namely, the very widespread extent of the lesion. At the same time, the clinical and pathological advantages gained by emphasising in our terminology which particular component of the kidney has been mainly affected have not been forgotten.

The difference between what I have called general and local glomerulo-nephritis is only a question of degree, namely, the number of glomeruli affected. It is said that successive reports on the state of the cardiovascular system provide a measure of this factor. Upon this topic, which is, I think, relatively of small importance, a voluminous literature must be consulted; I have summarised it by accepting the view that Heubner's[13] pædonephritis is the same condition as Volhard and Fahr's focal glomerulo-nephritis.

2. METHODS OF INVESTIGATION.

Reference to Table C will give at a glance the general scheme of investigation followed, though it will be obvious that for certain cases it was necessary, on medical grounds, to exercise discretion in the application of tests. Furthermore, it is well recognised that difficulties encountered during the investigation of renal cases are more frequent and more insurmountable

in children than in adults. For instance: (1) urine collection without catheterisation may be impossible; and the total volume in 24 hours is often inaccurately recorded even in older children; (2) blood vessels are small and one may have difficulty in obtaining blood for examination: in some cases I used the patient's saliva for the estimation of urea; (3) emotional disturbances are frequent in children; therefore blood pressure records are often not reliable; (4) accurate dieting is a great difficulty; one cannot expect the co-operation from a child which one receives from an adult.

For these reasons, tests were sometimes unsatisfactory; and sometimes the delay between repetitions of the same test was longer than one would have wished.

TABLE C.

PLAN OF INVESTIGATION.

1. *Medical history* of patient and of relatives.
2. *General clinical examination*, with special reference to
   - Body-weight.
   - Œdema.
   - Anæmia.
   - Heart and blood vessels. B.P.
   - Optic fundi.
   - Septic foci, *e.g.*, teeth and tonsils.
3. *Urine*. Daily Examination.
   - (*a*) General. Volume: sp. gr.: reaction.
   - (*b*) Chemical. Protein content.
     Urea content.
     Chloride content.
   - (*c*) Microscopical.
4. *Blood*. Nonprotein nitrogen.
   Wassermann reaction.
5. *Renal efficiency tests*.
   - (*a*) Phenolsulphonephthalein excretion.
   - (*b*) Urea concentration test.
   - (*c*) Salt test.
   - (*d*) Fixation of specific gravity test.
6. *"Living kidney" examination*.
7. *Autopsy. Histology.*

The following notes are supplied in amplification of the scheme shown in Table C:—

Urine. For some time I estimated the diastase content of urines daily, but later discarded this test. The chloride content was estimated by Harvey's modification of Volhard's method (*see* Myers [26]).

Blood. Non-protein nitrogen was estimated by a modified Kjeldahl process, with subsequent nesslerisation and colorimetric comparison.

Renal Efficiency Tests. From the outset one kept in mind the limitations which workers on adults have shown to exist in the use of these tests, as well as the caution which must be exercised in making deductions from the results obtained. For instance, it is not yet accurately known which particular functional capacity of the kidney is tested by the different functional tests. Furthermore, it must be remembered that in health no single activity of the kidney is exerted to the full: the organ possesses what may be described as a big "reserve power" and frequently no evidence of functional incapacity is revealed until damage is widespread and severe. In other words, the kidney conceals its own weaknesses at a time when the physician wishes to discover them; and when the lesions are no longer small enough to be hidden, obvious clinical signs frequently appear.

Another difficulty lies in the fact that the functional efficiency of kidney tissue which has developed by compensatory hypertrophy is unknown. Moreover, the functions of the kidney are disturbed by most severe diseases of the viscera, especially of the heart, blood vessels, lungs and blood; as also by all so-called "general diseases," for instance, fevers. Hence impairment of function, as shown by efficiency tests, may be only the shadow and not the substance. Wilcox and Lyttle[33] and Gittings and Græme Mitchell[11] give interesting figures in relationship to this aspect.

In healthy children the two-hour excretion of phenolsulphonephthalein, administered intramuscularly, should be at least 60%. L. W. Hill[14] found it to be 76%, Leopold and Bernhard[16] 70%, Curtis[6] 75%, Tileston and Comfort[30] 80%, and Wilcox and Lyttle[33] 60%. When œdema is present, the test by intramuscular route is almost valueless; and when there is blood in the urine the estimation of the excreted dye is generally impossible. On several occasions I found the matching of colours in measuring the excreted 'phthalein a very difficult matter even when there was no blood in the urine; the addition of alkali to bring out the colour of the dye precipitates phosphates, which interfere with the colour comparison. The phosphates may be separated, but this renders the test less accurate. The urea concentration test was carried out according to the method described by McLean[18], except that the dose of urea employed was 10 grams. By the term "salt test" I refer to the exhibition of 10 grams of sodium chloride, with subsequent investigation of increase of weight, due to œdema, and of the urinary excretion of salt. This test undoubtedly aggravates the patient's condition temporarily; it was used on a few occasions only.

The fixation of specific gravity test was found to be applicable only to the older children; I have little experience of it.

" Living Kidney " Examination. In certain cases, decapsulation of the kidneys was performed, and I am greatly indebted to Mr. R. C. Dun, Senior Surgeon to the Royal Liverpool Children's Hospital, for his kindness in assisting me by excising a small wedge of kidney substance during the operation. This piece of tissue was dropped at once into formalin and was later examined microscopically. By this method of examination a fuller knowledge of the kidney lesion is gained.

3. Description of Cases Studied.

During the past three years I have had the opportunity of observing some 20 cases of nephropathy in children between the ages of 2½ and 12 years. One of these cases has been published under the names of Dr. Dingwall Fordyce and myself[10] and I shall not include it in this paper.

Four other cases could not, for various reasons, be studied adequately, and I have excluded them from this survey.

Of the remaining 15 cases I have classified three as acute glomerulo-nephritis, six as chronic glomerulo-nephritis, and six as diffuse tubular nephritis.

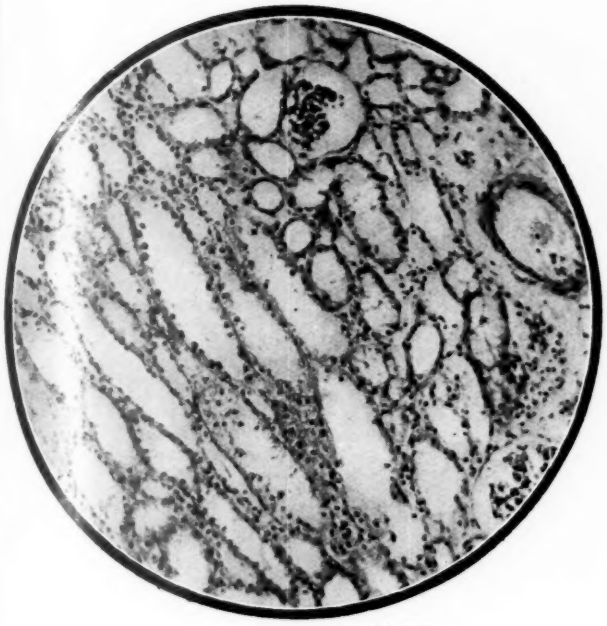
A. *Acute Glomerulo-Nephritis.*

Only brief reference will be made to these three cases.

M. D. Female, age 3¼ years. For some weeks before the onset of nephritis this child had been debilitated; there had also been otorrhœa and a vaginal discharge. An eruption resembling " points of blood " was noticed on the body and legs two weeks before the child was brought to hospital suffering with pyrexia, oliguria, hæmaturia and proteinuria (7 gms. per litre). There was a moderate grade of œdema of the subcutaneous tissues; and numerous impetiginous areas were scattered widely on the skin. Microscopical examination of the urine showed numerous casts of all descriptions The extreme gravity of the patient's condition made systematic examination impossible. The systolic blood pressure was about 90 mm. of mercury; possibly this is too high an estimate because the child was in an irritable, frightened state. She died a few days after admission and an autopsy was refused. There does not appear to be sufficient evidence to say that nephritis was secondary to impetigo, though this is probable.

D. S. Male, age 2½ years. Oliguria and hæmaturia developed immediately after pneumonia. The urine contained 2 to 3 gms. of protein per litre and numerous casts were found. The temperature on admission was 103°, but it fell to normal almost at once and recovery was rapid. When the patient was re-examined 12 months after his attack, his general health was quite satisfactory, the urine was normal and the systolic blood pressure was 112 mm. of mercury. This is a high figure for a child of 3½ years.

A. D. Male, age 9 5/12 years. In infancy this child had been circumcised and had had slight measles. There was no illness preceding the attack of nephritis, except a " cold in the head." The onset was characterised by rise of temperature, vomiting, and pain in the right side of the abdomen: these signs, together with anorexia and very slight jaundice suggest that a catarrhal cholangitis had developed. Proteinuria, up to 1 gm. per litre, was discovered: erythrocytes and leucocytes were present in the urine, but no casts were found. Slight œdema of the ankles was noted. The blood non-

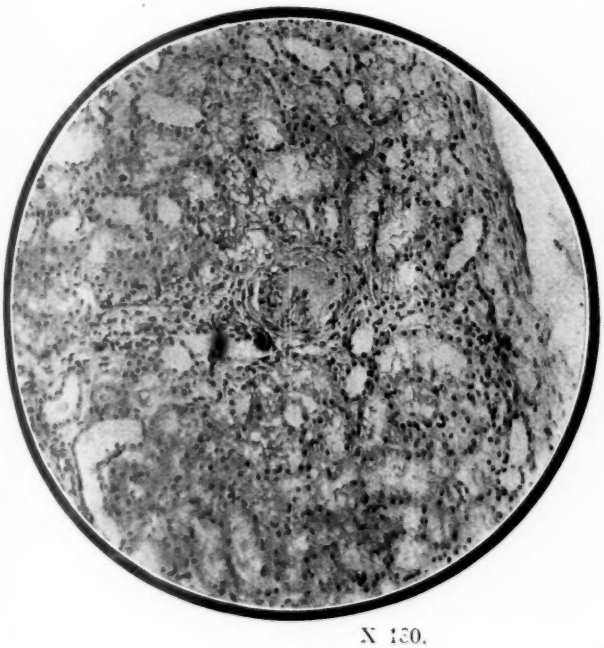


X 135.

Fig. 1.

X 135.

Fig. 2.



X 130.

Fig. 3.

X 135.

Fig. 4.

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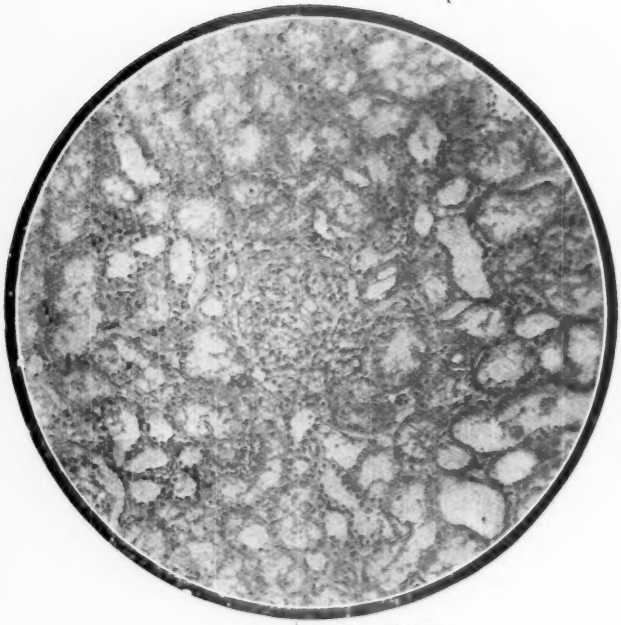
X 135.

Fig. 5.

X 200.

Fig. 5a.



X 125.

Fig. 6.

X 150.

Fig. 7.

protein nitrogen was 37 mgs. per 100 c.cms. of whole blood, and the two-hour 'phthalein excretion was 94%. Recovery was rapid; and when the patient was re-examined $1\frac{7}{12}$ years after this attack he was found to be in normal health, and his urine was normal. The systolic blood pressure was 117 mm. of mercury (age of patient $11\frac{1}{4}$ years).

B. *Chronic Glomerulo-Nephritis.*

This form of nephritis affects especially children of school age. The onset may be sudden, with an acute nephritis, or it may be gradual. In either case the disease is frequently preceded by one of the exanthemata, or by some infective condition, for instance, tonsillitis, to which special attention has been drawn by many observers, including Cautley[5], Marriott[21], Allison[1], and D. L. Smith and C. W. Bailey[29].

When the onset is insidious, anorexia, headache, vomiting, oliguria and hæmaturia are frequent symptoms; œdema is variable in degree, but is generally not a prominent sign except during an acute exacerbation. Pallor and general malnutrition are almost always found. Some cases bear a striking resemblance to tuberculosis of the kidneys and urinary tract.

The following are abbreviated records of my cases; additional notes will be found in Table D:—

M. S. The patient had whooping-cough, chicken-pox, measles with pneumonia, and severe scarlet fever, all during one year. Bilateral otorrhœa developed as a complication of scarlet fever, and the mother noticed that the urine was becoming scanty and dark coloured. Headaches, anorexia, general malaise and some œdema of the face, body and legs were additional complaints. The parents noted that the symptoms showed cyclical exacerbations, each attack lasting about two weeks. Œdema soon disappeared and has not redeveloped at any time. She is a thin, frail, nervous child; her teeth and tonsils are not above suspicion.

G. R. Parents are Russian Jews; healthy. The patient had whooping-cough, chicken-pox, measles and mumps in early childhood. Adenoids removed at 3 years.

No illness immediately preceded the present complaint, which began with cough, anorexia and vomiting; also slight pains in the chest and abdomen on exertion. There was some headache, fever and sweating. The urine was noticed to be dark coloured. Shortly after the onset, right-sided pleurisy with effusion developed. The fluid was straw coloured and contained large numbers of small lymphocytes; neither tubercle bacilli nor other micro-organisms were discovered and cultures were sterile. Later, radiographs of the chest showed no evidence of tuberculosis. Von Pirquet reaction negative. Radiographic examination of kidney regions was negative. No tubercle bacilli were found in the urine or fæces; guinea-pig inoculation with urine was negative for tubercle bacilli.

The patient is a well-developed, fat boy with slight œdema below the knees. Teeth and tonsils healthy.

W. C. The patient had whooping-cough in infancy, hæmorrhagic measles when $6\frac{1}{2}$ years old and chicken-pox when $7\frac{1}{2}$ years old. He is stated to have bled freely after circumcision and after extraction of teeth. With the onset of tracheitis when $8\frac{4}{12}$ years old, the parents noticed that the urine was dark coloured; there was also some loss of appetite. Whenever he caught a "chest cold," which was a frequent occurrence, the urine became bright red, with increased frequency of micturition during the day, and there was anorexia and increased pallor.

Between these attacks the urine did not become normal in colour. He is a thin, frail, alert child of unusually high intelligence. No œdema has been noted. On

admission to hospital he was found to have calcareous lymphatic glands in the abdomen; these were confirmed by radiograph. There were no signs, clinical or radiographic, of tuberculosis elsewhere. Examination of the bladder by radiography and cystoscopy, and of the urine by microscopy and by guinea-pig inoculation, were all negative for tuberculosis. The teeth were satisfactory; tonsillectomy was required and was carried out in June, 1924.

E. D. The patient had not suffered with any previous illnesses except enuresis. The onset occurred with a "bilious attack," followed by puffiness around the eyes, and possibly by a purpuric eruption on the legs. The patient was a thin, pale, nervous girl, with spasmodic internal strabismus. There was no œdema. The teeth were satisfactory; but the tonsils were found to be unhealthy and were removed in December, 1923. Blood coagulation time and fragility tests were normal. No tubercle bacilli were found in the urine.

R. T. Fairly healthy family history. There was no known cause for the onset of hæmaturia in this patient; it began five weeks before admission to hospital and continued intermittently. Von Pirquet reaction was negative. Radiograph of the chest showed a good deal of spottiness of and adjacent to the right lung root. Radiographs of the kidney regions showed nothing abnormal.

C. R. The patient's previous illnesses were measles, one year before the present trouble, and frequent attacks of nocturnal enuresis. The complaint began with puffiness of the face which was noticed after an attack of scarlet fever; at the same time the urine was noticed to be dark red in colour. The appetite was greater than usual. The patient was found to be a fairly well-nourished, pale child, with slight œdema of the shins. Four very septic teeth were extracted and tonsillectomy was performed in May, 1924.

In the urine of these patients red blood corpuscles and leucocytes, hyaline, granular and epithelial casts were almost constantly present. Blood casts were less frequently seen. Epithelial cells, probably from the kidney tubules, were commonly found. It should be noted that the amount of protein passed in the urine in chronic glomerulo-nephritis is comparatively small. The optic fundi were normal in all cases. The cardiac dulness was normal in extent in all patients except G. R., in whom it was possibly increased ($3\frac{1}{2}$ inches from the mid-sternal line in the fifth intercostal space: age of patient at this time was 13 years). No case showed signs of organic heart disease.

It will be seen on reference to Table D that abnormally high blood pressure readings were observed in each child except R. T., in whom records were not made; but it must be pointed out that by the time G. R.'s systolic blood pressure was 180 mm. of mercury (age of patient=$13\frac{1}{4}$ years), his urine had become normal; and similarly when E. D.'s systolic blood pressure was 134 mm. of mercury (age of patient=$11\frac{7}{12}$ years), her urine was normal.

In attempting to determine the prognosis in cases of chronic glomerulo-nephritis it is important to remember that two processes, one progressive and the other regenerative, are probably taking place. The former includes epithelial inflammation, recognised by finding protein in the urine, and kidney sclerosis. So long as proteinuria continues one may assume that progressive inflammatory changes are taking place; improvement may be recorded when proteinuria is diminishing or has disappeared. Any

TABLE D.

GLOMERULO-NEPHRITIS.

Initials of patient	M. S.	G. R.	W. C.	E. D.	R. T.	C. R.
Sex	Female	Male	Male	Female	Male	Male
Age at onset of nephritis	$6\frac{3}{12}$ years	$11\frac{2}{12}$ years	$8\frac{4}{12}$ years	10 years.	8 years	7 years
Ætiology	Scarlet Fever	Unknown	? Tracheitis	"Bilious attack"	Unknown	Scarlet fever
Wassermann Reaction	Weakly negative	Negative	Negative	Negative	Weakly negative	Weakly negative
Blood-pressure (in m.ms. of mercury)	133:121:117:110	112:120:114:180	110 : 114 : 118 : 134	96 : 134	(not recorded)	94 : 115
Blood non-protein nitrogen (in m.gms. per 100 c.cms. of whole blood)	55	31 : 32	51 : 39 : 42 : 38	35	45	25
Urinary protein (in gms. per litre)	Trace to 1gm.	Trace to $\frac{1}{2}$gm.	Trace to $\frac{3}{4}$gm.	$\frac{1}{2}$ to $2\frac{1}{2}$ gms.	$\frac{1}{2}$ to $\frac{3}{4}$ gms.	$\frac{1}{2}$ to $2\frac{1}{2}$ gms.
Phthalein excretion (total in 2 hours)	93%	49%	56% : over 65% : 77%	68%	Over 50%	Over 90%
Urea concentration test (a/1st hour : b/2nd hour)	a/2·5% b/2·5%	a/2·3% b/2·2%	a/1·3% b/2·0% : a/2·2% b/2·5%	a/2·8% b/3·2%	(not recorded)	(not recorded)
Duration of nephritis (to present date)	$4\frac{1}{12}$ years	$2\frac{2}{12}$ years	$2\frac{2}{12}$ years	$1\frac{7}{12}$ years	$1\frac{0}{12}$ years	$1\frac{0}{12}$ years
Result	Improving	? Cured	Improving	? Cured	Improving	Improving

The findings have been recorded in the above form in order to give as clear as possible a view of each case, and to permit comparison of cases. When several results of one test are given they are shown in chronological order. Duplicate but similar findings have been omitted in order to maintain simplicity.

TABLE E.

DIFFUSE TUBULAR NEPHRITIS.

Initials of patient	V. B.	W. L.	M. S.	A. S.	T. W.	J. E.
Sex	Male	Male	Male	Male	Female	Male
Age at onset of nephritis	? $7\frac{3}{4}$ years; probably earlier	4 years	5_{12}^{7} years	$2\frac{3}{4}$ years	2_{12}^{8} years	2_{12}^{11} years
Ætiology	Tuberculosis	Unknown	Unknown	Unknown	"General cold"	Whooping cough
Wassermann Reaction	Negative	Negative	Negative	Negative	Weakly positive	(not done)
Blood pressure (in m.ms of mercury)	128 : 145 : 135	109 : 110 : L : 115 : 105 : R : 112 : 120 : 128 : 115 : 116 : 118	95 : L : 98 : 95 : 94	95 : 75 : R : L : 88 : 104	85 : R : L	95 : 85 : 115
Blood non-protein nitrogen (in m.gms. per 100 c.cms. of whole blood)	92 : 104 : 108 : 59 : 68	35 : 32 : L : 41 : R : 38 : 45	36 : L : 32	37 : 39 : 37 : R : L : 37	30 : 33 : R : L	30 : 26
Urinary protein (in gms. per litre)	2 to 12 gms.	Up to 12 gms.	Up to 16 gms.	Over 12 gms.	Up to 11 gms.	8 to 12 gms.
'Phthalein excretion (total in 2 hours)	Very faint trace : ? 40%	81% : L : R : 64% : 42%	56% : L : over 80%	R : L : 74%	96% : R : L	82%
Urea concentration test (a/1st hour ; b/2nd hour)	a/0·64 b/0·67	a/1·0 b/1·1 : a/1·1 b/1·7 : L : R : a/1·7 b/2·0 : a/2·7 b/2·2	a/0·5 b/1·4 : L : a/2·2 b/3·1	a/1·8 b/2·9 : R : L : a/1·6 b/2·6	(not done)	a/1·6 b/1·8
Operation	None	Bilateral decapsulation	Unilateral decapsulation	Bilateral decapsulation	Bilateral decapsulation	None
Duration of nephritis (to present date)	? 4 years	2_{12}^{7} years	$1\frac{1}{4}$ years	3_{12}^{1} years	$1\frac{9}{12}$ year	3_{12}^{1} years
Result	Death in uræmia	Death	Death	Alive	Death	Alive

See footnote to Table D.

Decapsulation operations upon the right and left kidneys are shown by R and L respectively

effect which kidney sclerosis may have upon the cardiovascular system seems to depend upon the distribution and stage of the lesion; hence the blood pressure may or may not be raised in chronic glomerulo-nephritis. When it is permanently elevated serious kidney disease is present.

Regeneration of kidney tissue plays a greater part in the child than in the adult, and its effect in concealing the true extent of the pathological change is probably greater the younger the patient. In the two patients G. R.* and E. D. it is evident that at the time of the last urinary examination there was no active kidney inflammation; but the histories of the cases, together with the blood pressure records, furnished proof sufficient to classify them as chronic glomerulo-nephritis. If they had been examples of local glomerulo-nephritis, alternatively termed Volhard and Fahr's focal nephritis and Heubner's pædonephritis, the blood pressure would not have been higher than normal [Heubner[13], Tripputi[31] and others]. Mendel[23] has pointed out that since the time when Heubner gave his original description of pædonephritis it has been shown that this syndrome has not the clear cut boundaries which it was at first believed to possess. I submit that if the term pædonephritis is to be retained it must be regarded as a mild form of chronic glomerulo-nephritis, and not as a separate entity. There are obvious disadvantages in introducing new words to differentiate cases which seem to vary only in the extent of the lesion.

The possibility of a recurrence of acute nephritis in these cases is considerable; and Emerson[8] has emphasised that even minor symptoms may be of grave significance, because they furnish evidence of advancing epithelial disease. Hence it is most difficult to say when a case of chronic glomerulo-nephritis is cured. Even if there has been no active inflammation for several years, it is possible that delayed vascular complications may appear in adult life.

C. *Diffuse Tubular Nephritis.*

The most striking feature of this form of nephritis is severe generalised œdema. The age of the patient is usually younger than in chronic glomerulo-nephritis. Cold and exposure have always been regarded as ætiological factors; at times tuberculosis, syphilis and chronic suppurative conditions are antecedents. Marriott[21] finds that staphylococcal infection of the nasal sinuses is often the primary cause. The onset of the disease is generally insidious, with pallor, oliguria and œdema. Pyrexia is often only slight; sometimes it is absent. Hæmaturia is seldom noticed. Proteinuria is considerable, and many casts of all descriptions—especially hyaline, granular, epithelial and fatty—are found in the urine. Leucocytes and cells from the renal tract are numerous. Erythrocytes are scanty.

*A few days before the completion of this paper, the patient G. R. suffered an acute exacerbation of nephritis, characterised by general malaise, oliguria and hæmaturia, with numerous urinary casts.

Retention of nitrogen in the blood is infrequent; but the power of chloride elimination is considerably diminished. The blood pressure is not raised and the heart is not hypertrophied. There are no changes in the eye grounds. Death is frequently due to some intercurrent infection.

Attention must be drawn to the fact that the newer conception of this condition makes it a " general metabolic disturbance " rather than a local kidney disorder with secondary œdema.

Linder, Lundsgaard and van Slyke[17] have emphasised the great fall in concentration of plasma proteins found in this disease; and Clausen[4] has noted the lowering of surface tension, both of the blood and of the urine. Furthermore, this observer has shown that the substance which has this effect can increase the permeability of collodion membranes for protein.

At autopsy the kidneys are generally found to be of the large, pale variety, with or without amyloid degeneration. The cortex is wider than normal and is of a light yellow or light red colour; it is clearly differentiated from the medulla. Further reference to the pathology of this condition will be made later.

It is for this form of nephritis that Edebohls'[7] operation of bilateral kidney decapsulation has been most strongly advocated; and there is evidence to show that improvement sometimes follows this procedure, though the actual effect of the operation on the kidneys is not properly understood. Edebohls (*loc. cit.*) believed that decapsulation allowed new blood vessels to grow from the perinephric tissues into the kidneys. He was aware of the fact that after decapsulation a new capsule develops—in fact he recommended re-decapsulation if the patient's symptoms began to return after temporary improvement; but he held that the new capsule becomes organised in from three weeks to three months, and that it is always more succulent and vascular than the original capsule. Other observers have demonstrated that the new capsule formed after decapsulation is avascular* and that any beneficial effects following the operation must rather be ascribed to the relief of kidney tension. This hypothesis may be appropriate to cases of acute nephritis, but it is unlikely that increase of kidney tension is an important feature of subacute and chronic nephritis. Edebohls reports that he never noticed any evidence of increased renal tension in cases of chronic nephritis.

These difficulties have been discussed in a review of the subject of decapsulation in " Medical Science "[22] and also by J. Lovett Morse[24]. It is probable that renal decapsulation would give better results if performed earlier in the history of the case. The practical difficulty lies in selecting

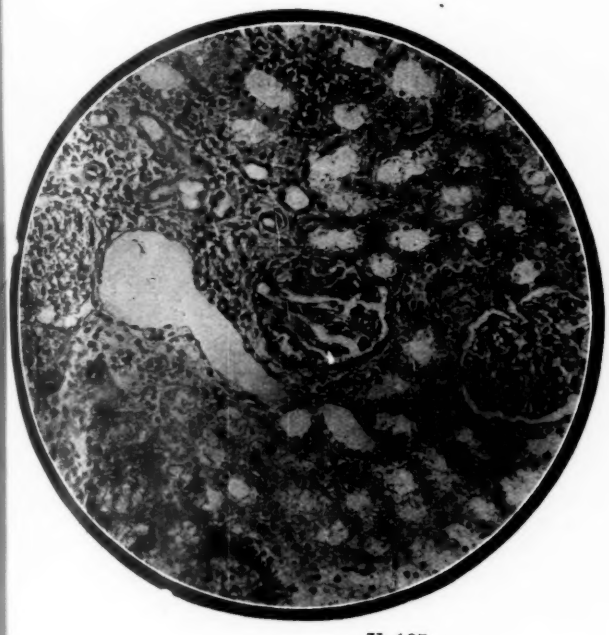
*There is much truth in the contention of Edebohls that since most of the experimental work on this question was carried out on the kidneys of normal, or acutely nephritic animals, the findings cannot properly be compared with the results in chronic nephritic human kidneys. As yet the reports on human cases are very few.

X 200.

Fig. 7a.

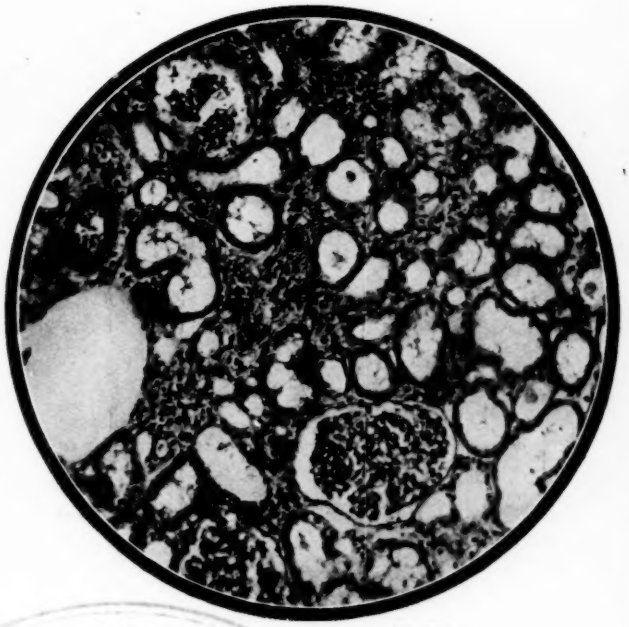
X 125.

Fig. 8.



X 135.

Fig. 9.



X 150.

Fig. 10.

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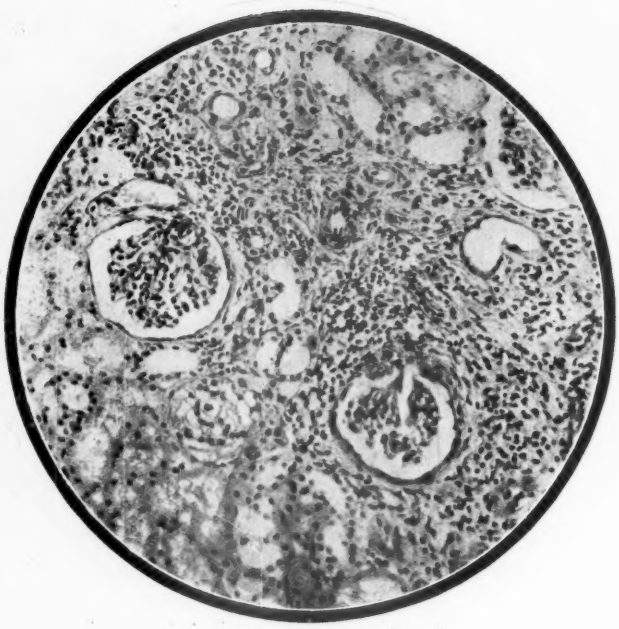
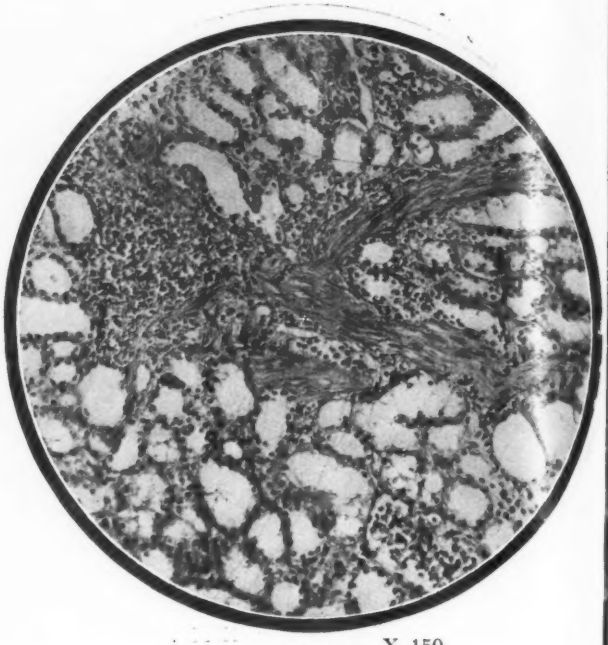


X 135.

Fig. 11.



X 150.

Fig. 12.

X 125.

Fig. 13.

X 125.

Fig. 14.

those cases of acute and early subacute nephritis which will not recover under medical treatment alone. Until we are able to do this it is unlikely that renal decapsulation will be extensively employed except as a last resource.

The operations upon the cases here reported were performed by Mr. R. C. Dun, who decapsulates only one kidney at a time and allows about one month to intervene between the two operations. He believes this procedure to be safer than the double operation. Four patients in this series underwent decapsulation; in one case it was unilateral only.

The following are brief notes of my own cases; additional details will be found in Table E:—

V. B. This boy came under observation at the age of 10 years. His father had died of phthisis when the patient was 11 months old; seven months later a tuberculous abscess developed on the right side of the boy's face. At the age of 2 years tuberculous dactylitis was diagnosed. Two months later the left knee joint was similarly affected and discharged through several sinuses. It is certain that the patient's kidneys were diseased by the age of $7\frac{3}{4}$ years; probably they were affected some considerable time before this.

When the child came under my observation he had been œdematous for about five weeks; the other chief symptoms were anorexia, lethargy, oliguria, headaches, epistaxis, vomiting and diarrhœa. He was found to be a very pale child, with numerous scars and bone deformities due to former tuberculosis. There were some carious teeth, and the tonsils were enlarged and slightly inflamed. The submaxillary and axillary lymphatic glands on both sides were enlarged. The heart was hypertrophied, the deep cardiac dulness being in the fifth left intercostal space four inches from the midsternal line; the second aortic sound was accentuated. Ascites and slight bilateral hydrothorax were present in addition to generalised subcutaneous œdema.

The child improved under treatment (note diminution of non-protein nitrogen of the blood); this suggested that the symptoms were largely due to an acute exacerbation of nephritis in kidneys affected by chronic changes, probably with amyloid degeneration. At a later examination the spleen was found to be palpable.

One week before death (age $11\frac{5}{12}$ years) the patient was re-admitted in uræmia, with severe headaches, oliguria and vomiting as main symptoms. Œdema was scarcely noticeable; several uræmic convulsions, with increasing drowsiness, ushered in the end. Unfortunately it was not possible to obtain permission for an autopsy.

W. L. Onset of orbital œdema when 4 years old. It was variable in degree. Some months later albuminuria was discovered. The patient was admitted to a hospital when $4\frac{5}{12}$ years old and was diagnosed "chronic nephritis"; treatment included laparotomy for suspected tuberculous peritonitis. Some ascitic fluid was liberated and enlarged mesenteric glands were noted.* When $4\frac{5}{12}$ years old the patient contracted measles, which caused an exacerbation of œdema.

He was first admitted to hospital at the age of 5 years; and on four subsequent occasions he was re-admitted with exacerbations of nephritis. Œdema was generally severe. Several carious teeth were removed. The tonsils were slightly hypertrophied, but were not removed. The urine was always negative for tubercle bacilli: on one occasion a growth of non-hæmolytic streptococci was obtained and the patient received a course of autogenous vaccine. The heart was normal; occasional bronchitis developed. The liver border was palpable $1\frac{1}{2}$ inches below the subcostal margin in the right nipple line. Its surface was very slightly granular. The eye grounds were normal.

* Within the last few weeks I have seen a younger brother of this patient suffering with advanced tuberculous peritonitis.

The first decapsulation was performed $1\frac{9}{12}$ years after the onset of symptoms. The left kidney was found to be enlarged and deep red in colour; but it must be remembered that the depth of colour noted at operation is undoubtedly influenced to some extent by traction on the kidney pedicle during the process of bringing the organ into the wound. The kidney capsule was thin and was easily stripped; it was not excised. Perinephric œdema was fairly considerable.

At the second operation (right kidney) the findings were similar to those recorded above. There was only slight bulging of the kidney substance when the capsule was incised; and the perinephric tissues were less œdematous than on the left side. A small wedge of kidney substance was removed for histological examination.

During the four months following the second operation there was undoubted improvement in the patient's general condition; œdema diminished to the extent of being a slight puffiness of the face only, the skin colour improved, and the only symptom was some lethargy. Then the former symptoms returned; œdema increased, and after a fluctuating course the patient died in his own home nine months after operation. It was not possible to perform an autopsy.

M. S. The patient's previous illness was measles, without complications, about two years before the onset of nephritis. This disease began when the child was $5\frac{7}{12}$ years old, with gradual swelling of the abdomen and external genitalia. Soon œdema of the face, hands and legs developed. Except for occasional slight frontal headache there were no other symptoms of any kind. Clinically there was much œdema, including hydrothorax and ascites. Pyrexia occurred from time to time. The heart was normal. Fourteen carious teeth were removed. The tonsils were slightly hypertrophied; and the eye grounds were normal.

The left kidney was decapsulated 11 months after the onset of symptoms. It was of normal size, with fairly deep sulci, and showed a few pale areas. The capsule stripped easily except at the sulci. Eighteen days after operation his condition showed no œdema of the face and only slight puffiness below the knees; skin colour was healthier and the patient much more comfortable. Some bronchitis was present. Table F shows the results of salt excretion tests carried out before, and one month after, unilateral decapsulation. It is obvious that these tests alone do not demonstrate that the improved power of excreting sodium chloride was due to unilateral decapsulation, but the findings are thought to be of sufficient interest to be recorded.

Decapsulation of the other kidney was deferred on account of recurring and irregular pyrexia which lasted about a week. It was decided to allow the patient to return to his own home, on strict diet, for a short period before undergoing the second operation. Unfortunately during this interval he became acutely ill with high fever, very intense œdema, vomiting, diarrhœa and headaches. He did not respond to treatment. On the day before his death, blood culture showed a pure growth of pneumococcus (proved bile-soluble).

Full post-mortem examination was carried out and showed a terminal pneumococcal peritonitis with a slightly turbid effusion. The wall of the left ventricle of the heart was $\frac{3}{8}$ inch thick. The lungs, which were compressed by pleural effusion, showed no gross disease. The spleen weighed $4\frac{1}{2}$ ounces. The kidneys are described later.

A. S. The patient had suffered no illnesses prior to the onset of orbital œdema, which began at the age of $2\frac{9}{12}$ years, and alternately disappeared and re-appeared about six times before the patient was admitted to hospital. The only other symptom was oliguria. At no time was blood seen in the urine. Clinically, generalised œdema was the most prominent feature. The heart and lungs were normal. The edge of the liver was palpable one inch below the right subcostal margin in the nipple line; its surface was smooth. The eye grounds were normal. No tubercle bacilli were found in the urine, but a free growth of streptococci was cultured on one occasion.

TABLE F.

Showing results of salt excretion tests carried out on M. S. (A) before decapsulation, and (B) one month after unilateral decapsulation.

	Date.	Weight in kilos.	Vol. of urine in c.cms.	NaCl percentage in urine.	Increase in NaCl percentage.	Total urinary NaCl in gms.
	12/13-3-23	25·27	—	0·0	—	—
A.		10 gms. NaCl given by mouth on 13-3-23.				
	13/14-3-23	26·3	1083	0·0	0·0	0 0
	14/15-3-23	—	1140	0·06	0·06	0·68
	15/16/3/23	—	1282	0·35	0·35	4·48
		Total urinary NaCl excretion in 24 hours 0·0 gms.				
		,, ,, ,, ,, ,, 48 ,, 0·68 ,,				
		,, ,, ,, ,, ,, 72 ,, 5·16 ,,				

	Date.	Weight in kilos.	Vol. of urine in c.cms.	NaCl percentage in urine.	Increase in NaCl percentage.	Total urinary NaCl in gms.
	16/17-4-23	Uncertain owing to surgical dressings	798	0·5	—	—
B.		10 gms. NaCl given by mouth on 17-4-23.				
	17/18-4-23	,,	912	1·04	0·54	4·92
	18/19-4-23	,,	712	·63	·13	·92
	19/20-4-23	,,	684	·59	·09	·61
	20/21-4-23	,,	684	·93	·43	2·94
		Total urinary NaCl excretion in 24 hours 4·92 gms.				
		,, ,, ,, ,, ,, 48 ,, 5·84 ,,				
		,, ,, ,, ,, ,, 72 ,, 6·45 ,,				

The first decapsulation operation was performed on the right kidney $\frac{8}{12}$ year after the onset of symptoms. The kidney capsule was found to be slightly more adherent than usual to the perinephric tissues, which were very œdematous. For four days following the operation the child was unusually irritable; obliguria was marked and œdema increased. By the sixth day œdema had considerably diminished again and the patient's health had improved. There was progressive diminution of dropsy and increased flow of urine.

The left kidney was decapsulated one month after the right. This viscus was found to be remarkably pale: it was larger than the right kidney and its capsule stripped easily. The surrounding tissues were intensely œdematous. A small wedge of kidney tissue was removed from each organ for histological examination.

After the second operation there was a temporary exacerbation of symptoms, followed by progressive diminution of œdema, which had disappeared completely two months after the second operation. The patient now looked very pale and wasted, but he was cheerful in spirits. Two months' treatment at a Convalescent Home

followed; after which the patient returned to his own home, where he has remained for the past two years, with the exception of a short visit to hospital for tonsillectomy and extraction of five carious teeth. It is interesting to note that only slight and temporary œdema followed the operation of tonsillectomy under general anæsthesia.

The parents report that the patient's life is now cyclical, with increasing general œdema up to a point when diarrhœa, vomiting and polyuria occur. The œdema then vanishes quickly, leaving the patient very emaciated and hungry. Generally the progressive swelling takes about two months to reach its climax; by the end of the following two to three weeks all œdema has disappeared again. The patient remains in good spirits even when he is œdematous.

The parents are satisfied that since tonsillectomy and dental treatment, the above symptoms have been much less noticeable; and the boy's present condition (Fig. 17) is very satisfactory. He has very slight œdema below the knees; his nutrition is good and his colour is healthy. The heart is of normal size; the blood pressure is higher than normal. No ophthalmoscopic changes can be found. The urine contains 8 gms. of protein per litre; epithelial, granular and hyaline casts are numerous; erythrocytes are absent.

T. W. Both father (Chinese) and mother are healthy. The patient had suffered only one previous illness, when at the age of $2\frac{4}{12}$ years she lost consciousness for half an hour. The cause was unknown. From birth there had been continuous oscillatory nystagmoid movements of the right eye.

When $2\frac{8}{12}$ years old she had "a cold in the head" and was in bed for one week. Three weeks later anorexia, thirst, and swellings around the eyes developed. No change in the urine was at first noticed by the parents. Later diarrhœa, and swellings of the abdomen and ankles, with dysuria and oliguria, developed. The child was then admitted to the Royal Liverpool Children's Hospital. She was drowsy and irritable during examination. The skin was dry and pale. Well-marked generalised œdema was present, but there were no signs of effusions into the serous sacs. The heart was of normal size and the first cardiac sound was accentuated at all areas. It was impossible to examine the optic fundi satisfactorily on account of the extreme œdema of the eyelids, and the difficulty of handling the patient. After two months' treatment in hospital, the child developed rubella and was transferred to a Fever Hospital. She was readmitted at the age of $3\frac{2}{12}$ years with an acute exacerbation of nephritis.

The first decapsulation operation (right kidney) was performed five months after the onset of the primary attack; the viscus was larger and paler than normal and its capsule stripped easily. The left kidney was decapsulated six weeks later; this organ was found to be larger and paler than the right. Its capsule was adherent in one or two places and several small pieces of kidney tissue remained attached to the capsule when this was removed. A small wedge of kidney tissue for microscopical examination was excised from both kidneys.

The patient's condition remained unchanged. Severe general œdema persisted and marked irritability on even the slightest disturbance was a prominent feature. All urine was passed into the bed. These two facts made the case a very unsatisfactory one to follow.

The patient died six weeks after the second operation, and it was not possible to obtain permission for an autopsy.

J. E. The patient's previous illnesses were:—Tonsillitis, at 12 months, whooping cough, at $2\frac{11}{12}$ years, and occasional mild bronchitic attacks. The present illness developed gradually with slight but variable puffiness around the eyes; this dated from the attack of whooping cough, and had been noted by the parents for several months before the patient was admitted to hospital at the age of $3\frac{1}{2}$ years.

X 125.

Fig. 15.

X 135.

Fig. 16.

Fig. 17.

The child was pale but fairly well nourished. There was slight œdema of eyelids, hands and wrists, legs and feet; no signs of free fluid in the pleural or peritoneal cavities were found. The heart was normal. Slight bronchitis was noted and the tonsils were hypertrophied. Shortly after admission the patient had an attack of acute follicular tonsillitis, and Mr. P. W. Leathart considered that tonsillectomy would be required later. The teeth were sound. The patient improved and was discharged to his home almost free from œdema. He continued to attend the Out-Patient Department of the hospital. At the age of 3 $\frac{9}{12}$ years he passed through measles and broncho-pneumonia without any recurrence of œdema or other special kidney signs. In September, 1924 (age 5 years), the patient was in bed for five weeks with right-sided pleuro-pneumonia; again no special kidney signs were noted. With the exception of these illnesses the boy has enjoyed very good health. There have been no swellings or headaches; the sight is good and the optic fundi are normal.

Clinical examination at the present time shows the patient to be well nourished, free from œdema and of healthy colour. Several teeth which recently became carious have received attention. The systolic blood pressure is 115 mm. of mercury, which is high for a child of 5 $\frac{8}{12}$ years. The urine contains 8 gms. of protein per litre, with granular and hyalo-granular casts, and a few leucocytes and large round epithelial cells. No erythrocytes can be found.

4. Pathological Findings in Diffuse Tubular Nephritis.

Reference has already been made to the naked eye appearance of the kidneys at operation. At the autopsy performed upon M. S., who died 86 days after decapsulation of the left kidney, it was decided to remove this kidney intact with its peri-renal fatty tissues, in order to investigate histological changes resulting upon decapsulation. These findings are noted below. The right kidney was found to be enlarged (weight 5 ozs.). The capsular vessels were congested; the capsule itself stripped easily and no cysts were seen. The surface of the kidney was not granular. Cross section showed the cortex to be very pale in colour; the pyramids were only slightly paler than normal. There were no visible hæmorrhages. The bladder and ureters were normal. The histological appearances of the kidney wedges removed in different cases were sufficiently alike to permit a single general description of the condition.

The most prominent feature noted is advanced granular degeneration of the cells lining the secreting tubules (Fig. 1), which are dilated. Most of these expanded tubules are empty, but in some portions the secreting cells have been desquamated and the tubules are partially filled with their degenerated remains (Fig. 2). There are scattered areas of necrosis where groups of tubules have become entirely disintegrated. Many of the collecting tubules contain granular masses (casts) and their lining cells show cloudy swelling. The glomeruli show several different types of pathological change, in varying grades. Some are swollen and congested as the result of cellular infiltration with mononuclears and, to a lesser degree, with polymorphonuclear leucocytes (Figs. 2, 10); the glomerulus may almost fill the capsule of Bowman (Fig. 2). Occasionally a hyaline thrombus is visible within the tuft (Fig. 3). Exudation into the capsule of Bowman is frequently noted;

most often it resembles " streamers " passing between the tuft and the inner surface of the capsule (Figs. 1, 4). Some glomeruli show a further stage of the same process, with adhesion to the capsule (Fig. 6) and the formation of epithelial crescents (Figs. 7, 7a). The capsule may be lined by a thin hyaline deposit (Fig. 3); in some cases this is laminated (Figs. 5, 5a).

The most advanced stage of degeneration appears to consist of fibroblastic infiltration of glomeruli which have undergone some or all of the changes described above; the remnants of these tufts can be seen as semi-sclerotic masses (Figs. 5, 5a, 8, 9, 16). The fact that in places the glomeruli appear to be in closer juxtaposition than usual may point to shrinkage of the kidney. The connective tissue shows areas of infiltration with small round cells; fibroblasts, polymorphs and erythrocytes are less numerous (Figs. 5, 5a, 7, 7a, 9, 11, 16). These areas form more or less circumscribed zones, and the adjacent epithelial cells show advanced degrees of the changes previously noted. Newly-formed fibrous tissue may be seen scattered in sheaf-formation (Fig. 12); probably it is not yet contracting, because the tubules lying between its strands do not appear to be compressed.

The only pathological change noted in the portions of kidney capsule removed with the wedges of renal tissue was some slight thickening in patches. The larger blood vessels of the kidney showed no pathological changes. The kidneys removed from M. S. at autopsy demand special notes. The left kidney, which had been decapsulated three months previously, was hardened in its bed of surrounding fat and sections were examined microscopically (Figs. 13, 14, 15, 16). With the exception of thin fibrous strands (*see* Fig. 13) there is no newly-formed capsule. The peri-renal fat contains numerous blood vessels, but careful search did not demonstrate that any of these passed into the kidney substance. Comparison of these sections with the illustration of a case examined by Dr. John H. Larkin for Dr. Edebohls[7] shows most striking differences. In the latter case four months had elapsed between decapsulation and the death of the patient. It would seem unlikely that the new vascular capsule which Larkin figures could have developed in the extra month of life which the patient enjoyed, in comparison with my patient. Furthermore, it should be noted that the patient of Edebohls was an adult, and therefore less likely than a child of 6½ years to show reparative changes in her kidneys.

5. Treatment.

I do not propose to deal with all the well-recognised and accepted methods of treatment of nephritis. I shall draw attention to the following points only:—

(1) In diffuse tubular nephritis the diet should be rich in protein and should have a high calorie content.

(2) As diuretics for œdematous patients, alkalis and urea by mouth are undoubtedly of value. Calcium lactate has been advocated by Boyd[2] and calcium chloride by Keith, Barrier and Whelan[15]. I have used the former without success.

(3) The removal of septic foci, *e.g.*, teeth, tonsils, sinus disease, is of great importance in the treatment of the present attack and as a safeguard against recurrences.

(4) Parents must be warned of the possibility and danger of slight exacerbations, and must guard the child against chills, intestinal disturbances and mild infections generally. Too much emphasis cannot be placed upon the comparative mildness of the general symptoms which to the parent may be the only signs of progressive kidney disease.

(5) Decapsulation of the kidneys was followed by some temporary improvement in my cases; and one child (A. S.) has undoubtedly derived great benefit.

6. Summary and Conclusions.

1. I have suggested what appears to me to be a suitable clinical and pathological classification for the inflammatory kidney diseases of childhood.

2. I have reported my findings in a small group of cases.

3. On these findings I would say that:—

(*a*) Renal efficiency tests, while certainly to be commended on general principles as the rational procedure in investigation of disease, have not in my experience furnished any diagnostic information of importance [*see* Crawford[5]]. On the other hand they are sometimes of help in determining the degree of the lesion, and whether it is advancing or retrogressing. They are of most value in prognosis and in directing diet and treatment. The tests must be repeated and taken into consideration along with clinical and other laboratory findings.

It can be stated definitely that continued nitrogen retention is of importance and denotes serious damage; and that a persistently low 'phthalein excretion is also serious.

(*b*) Kidney decapsulation is worthy of further trial. It is probable that results would be better if the operation were carried out sooner.

My best thanks are tendered to the Medical Research Council for enabling me to carry out these investigations, and for defraying the laboratory expenses. With one exception the patients were studied in Dr. Dingwall Fordyce's ward at the Royal Liverpool Children's Hospital, and I am greatly indebted to him for his helpful advice. Dr. J. Murray Bligh kindly allowed me to study one of his cases (M. S.). I gladly acknowledge

the help which the following gentlemen have given in their own special departments: Mr. R. C. Dun, Professor E. E. Glynn, Mr. Thurstan Holland, Mr. F. A. G. Jeans, Dr. Howell Evans, Dr. P. W. Leathart, and Mr. P. G. Capons. The microscopical sections were prepared in Professor Glynn's laboratory.

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A CASE OF HYPERTELORISM.

BY

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Hypertelorism is the name given to a rare congenital cranio-facial deformity by D. M. Greig[2] who was the first to differentiate the condition from other deformities of the cranium. The chief characteristic of the condition is an excessive distance between the eyes producing an appearance reminiscent of that of the Fish-Footman in *Alice in Wonderland*. In a paper published in 1924 he describes two cases and gives a very full description of the skull of the more advanced case. So far as I know only six cases have been described, but no doubt the small number of the published cases is due to the condition having been undifferentiated from other deformities such as oxycephaly. I have myself seen three cases including one of Greig's. As the descriptions of the published cases are readily accessible, I shall not summarise the papers that have been published, but shall proceed at once to describe the case which is at present under my care.

Thomas R. Age, 11 years 4 months. Mental age, 5$\frac{10}{12}$. Intelligence quotient, 51. This boy was admitted to Baldovan Institution on 16th January, 1926. He is the older of two children. His parents are normal physically and mentally, except that his mother is said to have had a goitre for four years. She has not been seen by the writer. Her husband states that the goitre is not very large, but becomes larger when she is agitated; that she is nervous, has a quick pulse, and often complains of palpitation or of "her heart stopping"; that there is no undue prominence of her eyes. During her pregnancy she was in good health, but her legs became much swollen before the child's birth, so that she often had to lie down in the afternoons. The child's birth was normal, and he was nursed at the breast, but he was a delicate baby and did not sit up till he was 2 years of age nor walk till he was 4 years old. He was operated on for rupture at the age of 2, but the operation was unsuccessful, and was repeated last June with success. He wears no truss.

He is a fairly healthy-looking child, but is very small for his age, his height being 3 ft. 9$\frac{1}{4}$ ins., and his weight 3 st. 4 lbs. This is approximately eight inches less than the average height for his age, and 26 lbs. less than the normal weight. He appears to have a large head. As a matter of fact the circumference of his head is slightly below the average for a boy of his age, but is decidedly above the average for a boy of his height—say an average boy 6$\frac{1}{2}$ years of age. The circumference of his head is 21$\frac{1}{2}$ inches and is the same as that of his chest; whereas, at his age, the chest measurement should be at least two inches greater than that of the head. The forehead is somewhat square, and the frontal eminences prominent, there being a suggestion of a vertical groove or hollow down the centre of the forehead reappearing at the tip of the nose. The bridge of the nose is broad and flat.

The most remarkable feature, however, is the abnormal distance between the eyes. The distance between the pupils, when the child is looking directly forward, is 2$\frac{3}{4}$ inches as compared with 2$\frac{1}{4}$ inches in an adult. The distance between the inner canthi is 2$\frac{1}{4}$ inches. The eyes are very slightly prominent, and although the child *can* look directly forward there is usually a slight external strabismus of the right eye. Convergence on near objects is imperfect, but is fairly good if his interest is excited,

In Greig's first case the skull was brachy-cephalic (index 82) with "a low forehead, a pronounced vertex rising more posterior to the bregma than usual, and a flat occiput." These features are not observed in the present case, where the cephalic index is 79·9, the forehead is fairly high, and the antero-posterior configuration of the skull is normal.

The mouth is small. The palate is high and narrow. The tongue is large and slightly fissured as in tongue-sucking children. The lower jaw is prognathous and the lower incisors bite in front of the stumps of the upper incisors. He has had 28 teeth, but four premolars are absent, and four teeth, including the two upper central incisors, are mere stumps.

The hands are of fair size. The skin is thick and soft and the hand reminds one of that of a Mongol, but the fissures on the palms do not have the arrangement which has lately been described as characteristic of Mongols. The feet, also, are soft and the forepart of the foot is remarkably broad.

Fig. 1.
Patient at the age of 11 months.

There is no acro-cyanosis, and the circulatory system is apparently normal, but when the dentist was extracting a stump under a local anæsthetic, the patient's face became so intensely cyanosed that the operator was afraid to extract any more. The gum bled very copiously and the blood coagulated quickly.

The child speaks well and takes an intelligent interest in his surroundings. Probably he is a little more intelligent than his low I.Q. seems to indicate, his mental deficiency being associated with a certain amount of mental retardation. The Binet tests quite justifiably presupposes school attendance from the age of 5 or 6 years, and consequently a child who has had little or no school attendance is liable to be given a rating which does not do full justice to his real mental capacity. The reason the child has not attended school is that the father did not wish to send him owing to his peculiar appearance. The school medical officer saw him at home and apparently no suggestion was made that he should be sent to a special school or institution until his parents removed to town.

The illustrations show the appearance of the child at different ages, and the contours of the skull as traced by means of a cyrtometer.

As to the nature of the condition, Greig regards all the deformities of the skull results of the abnormal shape of the sphenoid bone. The *fons et origo mali* he states as follows: "An interference with development, going back early in embryonic life, present certainly in the chondro-cranium and perhaps in the mesoblastic tissue in

Fig. 2.
Patient at the age of about 4 years.

which the chondro-cranium is laid down, a result of that hereditary want of balance in development, which in families marked by Nature for extinction, brings forth the physically and mentally maimed and defective individuals whom we stigmatise as 'Degenerates.'"

There does not, however, appear to be anything in the family history of the present case, nor in that of most of the other published cases, to support

the view that the condition is due to a bad heredity. The condition is congenital, and results from causes acting at an early period of embryonic life, but there are good grounds for believing that monstrosities are liable to be produced by intra-uterine environmental causes acting upon the embryo. In short, the condition may be analogous to the teratological or fancy forms of fish which Tornier, and Stockard, have proved experimentally to result from the embryos being allowed to develop in insanitary conditions.

Fig. 3.
Patient at the age of 11½ years.

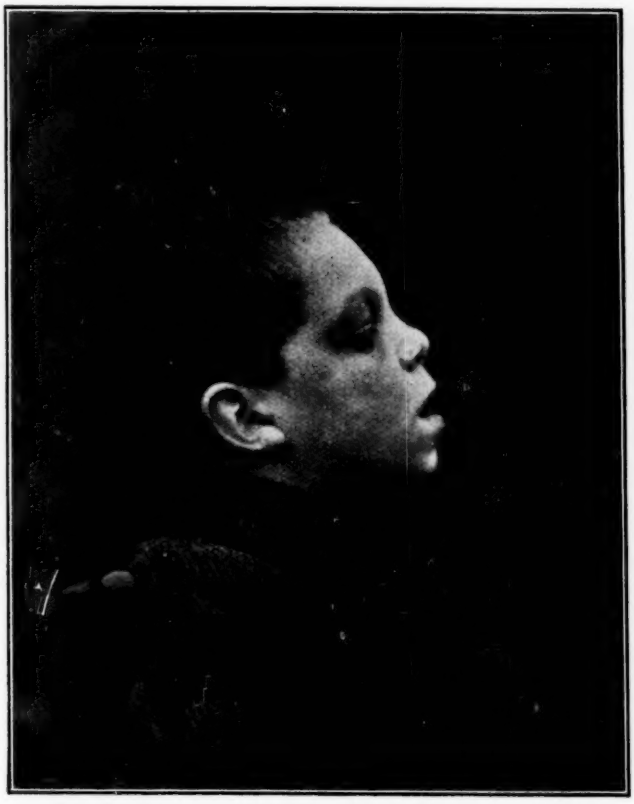

Fig. 4.
Patient at the age of 11½ years (profile).

For example, there is the variety of gold fish known as the " telescope fish " in which the eyes protrude from the sides of the head and the tail is doubled. According to Tornier, this is a mutation which results from weakening of the vigour of the germ cell by the abstraction of oxygen from the water during the first few days of its life. If hypertelorism may be explained as the result of some failure of nutrition and deficient oxygenation in early life, the other structural abnormalities present may be direct results of the same cause. It seems just as likely that the defective development of the brain indicated by the mental deficiency is to be accounted for in this way as that it results from the mechanical interference with its growth suggested by Greig.

CYRTOMETER TRACING OF HEAD.

(a) Antero-posterior.
(b) Greatest circumference.

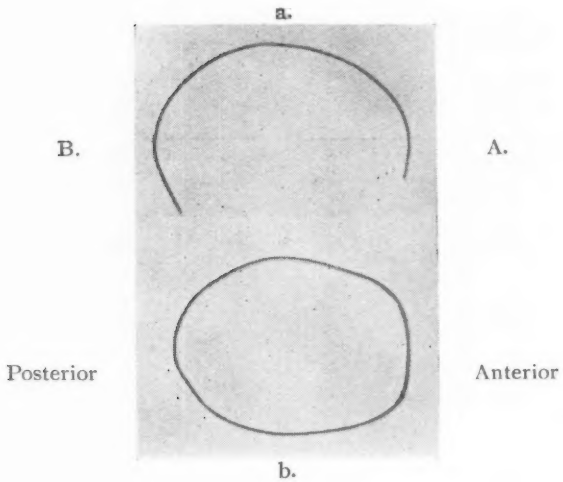

Fig. 5.

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A CASE OF HYPERTELORISM WITHOUT MENTAL DEFECT.

BY

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The name " ocular hypertelorism " has been given by Greig to a cranic facial deformity whose main feature is a wide separation of the orbits and their contents. He described two cases (both females) which he had had under observation for a number of years, and also the anatomical findings in the dried skull(2). The only other case in the literature which Greig could find was one described by Hutchison(3) as a case of oxycephaly, but which the photograph showed to be one of hypertelorism. Recently, Muir(4) recorded a case occurring in a female child of 13 months, and he discussed the anatomical findings of Greig's cases and his theory of production. More recently, Cockayne(1) described two cases, one, a female of 7 months, and the other, a boy of 6 years and 9 months. Cockayne came to the conclusion that there was nothing in the family history of these six cases to support Greig's theory as to a hereditary fault. It is noted that of these six cases five were females with gross mental defect. The sixth case (C. F. J. of Cockayne) is a male and it is stated that " mentally he is backward."

A. W., male, aged 4½ years. The present case shows no signs of mental backwardness. He is the elder of two children and was referred to my Out-Patient Department on account of bronchitis. His facial peculiarity was noticed; also that the mother had rather widely separated eyes. The father was seen some time later and it was noticed that he also had widely separated eyes with some flattening of the bridge of the nose. An old " family group " of the father's family was consulted and here the same tendency was obvious. A portion of this is reproduced (Fig. 1) showing the boy's father, uncle, aunt and grandfather.

The pregnancy and birth were normal. Although the parents noticed the boy's peculiar face, they did not pay any attention to it as he developed normally, sat up, walked and talked at the usual times.

Physically there is no defect except that the scrotum is empty and one testicle is in the inguinal canal. The fingers are rather short and tapering. He is also " pigeon breasted."

There is no mental defect, in fact, he is more than a match for children of his own age. The greatest horizontal circumference of the head is 505 mms., the greatest length from glabella to occiput 297 mms., and the greatest breadth from the level of the upper border of the pinna to a similar point on the other side 275 mms. The length of the head as measured by cephalometer is 176 mms. and the breadth 136 mms.

FIG. 1.

AUNT GRANDFATHER FATHER

Paternal side of Family of A.W.

FIG. 2.
A.W. æt. 4½ years.

FIG. 3.
Æt. 4½ years.

The cephalic index is therefore 77 and the head mesaticephalic. The length of the palpebral fissure is 32 mms., and the distance between the inner canthi is 41 mms. The palate is high and arched. The bridge of the nose is flattened and the nostrils look downward and forward (Fig. 2). Owing to the abnormal relative positions of the eyes, binocular vision is impossible and an alternating strabismus is present. There is a growth of downy fair hair on the back.

The examination of the fundus oculi revealed nothing abnormal. The Wassermann reaction was negative.

This boy is doubtless one of many similar cases of a mild degree of Greig's hypertelorism, and as he is not mentally defective, as in the cases already reported, these notes are presented.

Mr. Greig, in a private communication, agrees that this is a case of mild degree, and tells me that he knows of a similar case in which there is no mental defect. Added interest is also attached to this case as the parents (especially the father and his family relations) have widely separated eyes. As Mr. Greig states, there is no reason why a maldeveloped sphenoid should not be a familial occurrence and an exaggeration occasionally occur. This case would appear to lend support to Greig's view that the condition is the result of a hereditary want of balance in development in certain families.

Summary.

(1) A case of hypertelorism of mild degree in a boy of 4½ years is described.

(2) There is no mental defect.

(3) Attention was directed to the parents, and in both it was noticed that the eyes were rather widely separated. In the father there was some flattening of the nose in addition.

(4) Support to Greig's theory of a hereditary want of balance in development is given in this case.

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CHRONIC ULCERATIVE COLITIS IN CHILDREN.

BY

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By ulcerative colitis is meant in this paper a chronic ulcerative condition of the colon, inflammatory in nature, and accompanied by frequent loose motions containing blood and mucus.

Other conditions associated with a minor degree of acute ulceration occasionally are found in infants and young children, but in them the acute enteritis, rather than the few ulcers associated with it, dominates the picture. The disease, as characteristically seen in adults, is very rare in childhood, and the case herein described served to stimulate a search in the literature that has only yielded nine other proved cases, giving a total of 10 in all. Six other probable cases are added. Text books are reticent on the subject.

The rarity of the disease is proved by the additional fact that Helmholz, in his first account, could only find one other case, that of Logan, reported. Allchin in an address to the Royal Society of Medicine on the subject in 1908 stated: "I have never seen (in children) post mortem the appearance in the large intestine in any way resembling that which is constant in the disease (in adults)." Horder at the same meeting referred to six cases, all infants, aged 3, 4, 6, 8, 10 and 18 months respectively. Three of these were undiagnosed during life and four of the six had vomiting as well as diarrhœa; they therefore are not comparable with the chronic condition found in the case quoted below, the acuteness and absence of symptoms placing them in a different category.

Case.

Olga Y., aged 7, was admitted under the writer's care to the East London Hospital for Children, Shadwell, with the complaint of diarrhœa, the motions containing blood and mucus.

The disease began two years previous to admission with an attack of diarrhœa. This was not preceded by any other illness. Subsequently the stools remained loose, but became more frequent from time to time. The usual frequency for the 24 hours was about 4-6, and at the time of the exacerbation they rose to 10-12. There had not been any period of remission. The increase in number had been accompanied from the first by the presence of blood and slime. During exacerbations this became more marked. Abdominal pain was also present occasionally.

She was born in Egypt and lived there for the first two years of her life, an interval of three years intervening between this and the colitis. She had had chicken pox a few months before admission. There was no history of hæmaturia, diarrhœa or any other disorder. Her father had suffered from bilharziasis whilst in Egypt. There was no history of tuberculosis in the family.

Nutrition was fair (weight 3 stone 3 lbs.). The child was of a sallow complexion. There were no dilated venules on the cheeks. The head, neck and chest were normal in all respects. The abdomen was slightly full and a little tender on palpation, but not particularly so in any one situation. The liver and spleen were not palpable. The stools were fluid, unformed and contained little isolated flakes of yellowish fæcal material, some of them tinged with blood. Streaks of mucus streaked with blood were also present. The urine was normal, containing no blood or albumen.

The following pathological examinations were performed by Dr. Crawford.

Blood Count. R.B.C. 4,600,000; Hb. 60%; W.B.C. 12,000 (Eosinophiles 240 per c.mm.).

Examination of Stools (repeated three times). No non-lactose fermenting bacilli grown. No amœbæ or cysts and no bilharzia ova seen. Numerous red blood cells and pus cells present.

A sigmoidoscopic examination by Mr. J. E. Adams showed that the large bowel was severely diseased; a number of small ulcers were seen and the mucous membrane was thickened and bled readily. There were no polypi. A piece of diseased mucous membrane was removed and examined by Dr. Crawford. No parasites were seen in it, and no non-lactose fermenting organisms were isolated from it.

On this evidence it was assumed that the child was suffering from ulcerative colitis of the adult type.

Treatment.

She was confined to bed during the whole period of treatment.

Diet. At first she received Allenbury's Food (No. 2), milk, orange juice and three biscuits per diem. As improvement occurred this was changed to Allenbury's Food (No. 3), and custard and jellies were added. Finally when the stools began to look formed bread and butter, fish, potatoes and eggs were also given.

Drugs. On the analogy that a child has greater recuperative powers than an adult and on the grounds that she had already been treated unsuccessfully in three other hospitals, it was determined to push drug treatment energetically. The history of her birth in Egypt suggested that an infection by the bilharzia Mansoni or amœba histolytica was possibly at the root of the trouble in spite of the negative pathological findings and the interval of three years health. The pre-arranged programme was therefore to try the effect, in turn, of antidysenteric serum, emetine and antimony tartrate.

Anti-dysenteric serum was used, not because it was likely that bacilli would have persisted for such a period of time, but in accordance with Hurst's experience of its effect in ulcerative colitis of unknown ætiology. The colon was irrigated once daily with 1 in 5,000 flavine in normal saline, later with collosol silver 1 in 10,000. The change in her condition did not synchronise with the change in this local treatment. The serum was given on alternate days in doses of 30, 40, 25 and 50 cc.; it had no effect upon the number of stools or their looseness; the blood and mucus remained present in unchanged amount.

After ten days interval emetine hydrochloride gr. ½ per diem subcutaneously was given for four periods of three days, with an interval of three days between each period, and during this time emetine bismuth iodide gr. ii. was given three times per diem by the mouth. She received in all 6 grs. of emetine and 126 grs. of emetine bismuth iodide. After this course of treatment the stools became definitely fewer in number, but remained unformed and contained blood and mucus as before.

Ultimately, after a pause of 12 days, antimony tartrate in increasing doses was given intravenously, a week intervening between each injection; the doses were ½, 1, 1½, 2, 2½ grs. After the third injection blood and mucus had disappeared from the stools, and seven weeks after the first dose the child left the hospital. The motions were then formed, no longer fluid and contained neither blood nor mucus. Owing to the fact that she was then taken to Australia, whence enquiry has elicited no reply as to her subsequent state of health, it is impossible to say whether the cure has been permanent. Judging by all possible standards she was apparently well on discharge.

Analysis of the Recorded Cases.

In compiling the following table only proved cases of the condition have been included. The criteria used have been the presence of blood and mucus in the stools, diarrhœa and naked eye evidence of chronic disease of the colon. Radiographic evidence alone has been disregarded, as has a glazed appearance of the muscosa without ulceration.

CASE.	Sex & Age.	Onset.	Fever.	Hb. %.	Stool.			Proctoscope ? ulcers.	Duration (years).	Remissions.	Treatment.			Result.
					No.	Blood.	Mucus.				Operation.	Irrigation.	Transfusion	
1. Logan ...	M. 10	Acute	Considerable	50	3-5	+	+	+	—	0	0	Hot saline	0	Improved
2. Helmholz	F. 10	Acute	Low	60	8-10	+	+	—	$8\frac{1}{2}$	1 for 6 mos.	Cæcostomy	Saline	0	Cured
3. Helmholz	F. 11	Gradual	None	42	10-12	—	—	+	3	0	Ileostomy	Saline	+	Improved
4. Helmholz	M. 8	After Scarlet fever	Considerable	61	Frequent	+	+	+ P.M.	$1\frac{0}{12}$	1 for 17 mos.	Cæcostomy	—	+	Died
5. Helmholz	F. 15	Acute	—	81	5-6	+	+	+	$1\frac{10}{12}$	1 for 1 mon.	Appendicostomy	—	+	Died
6. Curtis ...	F. 6	—	Present	68	6-12	+	+	+	4	0	Ileostomy	Saline	0	Improved
7. Bourne...	F. 7	Gradual	Slight	60	4-10	+	+	+	$2\frac{1}{2}$	0	0	Flavine & Collosal silver	0	? Cured
8. Helmholz	F. 10	Acute	Considerable	50	7-8	+	+	+	2	0	0	0	+	Cured
9. Helmholz	F. 11	Acute	—	(Lowest 15—65)	5-7	+	—	+	2	0	0	0	+	Improved
10. Helmholz	F. 12	Acute	—	61	6-8	+[1]	+	+	1	0	0	0	0	Improved

0 = absent.
— = no information.

Symptoms.

It appears that the disease in children is of the same chronic nature as it is in adults. The shortest recorded duration was 14 months, the average nearly three years, and the longest 8½ years. There is nothing characteristic about the age incidence of the condition except that it does not seem to appear in infancy. Of the 10 cases seven were between the eighth and twelfth year, at the time of their coming under observation. Girls appear to be rather more liable than boys, the relative numbers being eight girls to two boys.

The symptomatology is characteristic and definite and is not distinguishable from that of the adult type of the disease. Diarrhœa with blood and mucus, abdominal discomfort, some degree of loss of weight and a considerable secondary anæmia, are the chief signs and symptoms. A low degree of fever was present at some time in five cases. In all of the tabulated cases proctoscopic examination showed an ulcerated mucosa. In six of the cases where a radiographic examination was made the appearances were characteristic. First, the lumen of the colon as a whole was definitely narrowed; secondly, the sacculi present in the normal colon were no longer seen. In eight of the 10 cases examinations of the stool for the presence of amœbæ and other protozoal parasites, for ova and for dysentery bacilli, were negative. In six tubercle bacilli were looked for without result. In three the blood serum was examined for the presence of agglutinins against dysentery bacilli and in one of them the result was a weak positive against Flexner's bacillus. Serum treatment here was without effect. The other results were negative. All cases had a definitely lowered hæmoglobin content of the blood. This averaged 60% for the 10 cases at the first examination, and in one a reading of 15% is recorded.

Remissions and Exacerbations.

All except one showed the presence of definite exacerbations. During these the stools became more in number and contained more blood and mucus, and the temperature became raised. Seven cases had no remission, three had one remission. These were as a rule for a period of about six weeks; one was for as long as 17 months. Two occurred in cases ultimately fatal.

Complications.

Transient arthritis (both knees) occurred in one case; abscess formation from direct extension into the right psoas region in one, and peri-rectal abscess in two; buccal and œsophageal ulceration (with perforation into the right pleural cavity) occurred once.

Result.

Two of the 10 cases died, one was cured, the remainder were improved, but not cured when reported upon. The writer's case was without symptoms or abnormal signs when last heard of.

TREATMENT.

Locally. Colonic irrigation with 1 in 5,000 flavine in normal saline or with hot normal saline appears to be of some use.

Operative. In four cases the bowel was brought to the surface with the idea of preventing fæcal irritation of the diseased colon, and of lavage through this from the opening. Cæcostomy was done twice and ileostomy twice. One of the former and both the latter operations were followed by improvement. Appendicostomy was done in one case and was eventually followed by death as was the other cæcostomy.

GENERAL TREATMENT.

Diet. A fluid diet consisting chiefly of milk appeared to be most easily tolerated, though Logan's case was better with a full diet. Food leaving residue is contra-indicated.

Drugs. There is no drug which stands out as being of value in this condition. Search must be made for any possible ætiological agent and the individual case treated on its merits.

Two measures other than local irrigation may be of use in dealing with the colonic condition, the administration of kaolin in half drachm doses, and a systematic and pathologically regulated attempt to flood out other intestinal flora by means of B. acidophilus.

Transfusion, appears to be a valuable means of treating the secondary anæmia which is sometimes severe. It was followed in two of Helmholz's cases by a striking improvement in the local symptoms also. The almost universally low hæmoglobin figures are argument enough to urge that this form of treatment be tried and even repeated.

CASES NOT YIELDING CONCLUSIVE SIGNS.

Besides these 10 cases whose authenticity is beyond doubt there remain the following seven cases purporting to belong to the group.

Cases I. and II. Cautley reports two cases, both boys aged 9, who had suffered from diarrhœa and the passage of blood and mucus. There is no report as to the proctoscopic condition, the microscopical examination of the stools, the presence of anæmia, or of fever. The duration was two years and fourteen months. Both cases were improved. Irrigation with silver nitrate was tried in one of them with some success.

Helmholz in his second account, besides the three cases included in the above table, describes four others.

Case III. (Case 2 of his paper). A boy aged 11 was brought with diarrhœa. The motions had been streaked with blood. The hæmoglobin was 76%. Microscopically the stool contained erythmocytes and pus cells, no parasites or ova. Proctoscopic examination revealed "the granular glazed mucosa generally associated with ulcerative colitis." The X-ray later "indicated ulcerative colitis." A transfusion of 400 cc. of maternal blood was followed by a great improvement.

Case IV. (Case 3 of his paper). A boy aged 8½ had similar symptoms. The hæmoglobin was 71%. Entamœba histolytica was found in one stool. Proctoscopic examination showed a "mild granular appearance of the mucosa." Radiographic examination later was definitely positive for chronic ulcerative colitis. Transfusion here again was followed by improvement.

Case V. (Case 4 of his paper). A boy aged 12 came with watery blood-streaked stools. Before admission "it was thought that an amœba" had been found. The hæmoglobin was 65%. The radiograph was "typical of chronic ulcerative colitis." Proctoscopic examination revealed diffuse hyperæmia of the recto-sigmoidal mucosa with the "typical granular glazed appearance of ulcerative colitis." The child was slightly improved by treatment.

Case VI. (Case 7 of his paper). A boy aged 7 complained of the passage of blood and mucus from the bowels. The hæmoglobin was 65%. The X-ray was negative. The proctoscope suggested a diagnosis of "granular proctosigmoiditis."

Case VII. Miller in an account of cœliac disease mentions under the head "Chronic enteritis of the dysenteric type" a case of a girl of 6. The onset was indefinite and the symptoms were diarrhœa and wasting. The stools contained mucus, pus and blood. No dysenteric organisms were found. Many relapses occurred and she died four months after discharge.

Cautley's two cases, the first three quoted of Helmholz and that of Miller appear to be cases of ulcerative colitis. The absence of ulceration in some of them is presumably a measure of their early or mild nature. The histories of the passage of blood, mucus and pus with diarrhœa, without other sufficient cause, when taken with the radiographic and sigmoidoscopic evidence, are suggestive. But in none of the seven is the evidence conclusive and in the last case of Helmholz it is frankly insufficient. The finding of amœbæ in two of Helmholz's cases is an interesting point, but the streptococci isolated from the stools of three others appear to be accepted by him as the causative organism upon very insufficient grounds.

Conclusions.

The clinical picture provided by the disease is one of continued fæcal irritation of the colonic mucosa rather than of a progressive destruction of that organ. The balance between destruction and repair is so nicely held that the disease may last for years. The continuous slight drain of blood and fluid and the absorption of toxins from the diseased surface add the remaining characteristics.

It appears to the writer that some primary occurrence takes place as a result of which the power of the colonic mucous membrane to resist the passage over it of the heavily infected fæces becomes impaired, with the result that continued local ulceration and consequent thickening and fibrosis occurs. What this primary occurrence may be it is not easy to guess. Presumably it is frequently an infection and possibly one that does its damage and sometimes dies. The effect of antimony in the writer's case, of antidysenteric serum as used by Hurst, and the finding of amœbæ in two of Helmholz's second series of cases all point to the possible truth of this supposition. The work of Bargen, who isolated a diplococcus from the

colonic mucosa of patients, inoculated it intravenously into rabbits and produced a disease similar to ulcerative colitis, needs more bacteriological and experimental confirmation, before acceptance. Whether in the case above recorded bilharziasis was the factor at the root of the trouble was never proved, but the fact that the patient had lived in Egypt, coupled with effect of antimony tartrate, is suggestive. It is conceivable that antimony tartrate is of use in the disease apart from any known ætiological factor, but this is a point that needs further proof. It would seem that if the unknown ætiological factor can be removed recovery is possible.

SUMMARY.

A case of ulcerative colitis in a child is recorded.

An analysis of 10 other proved cases found in the literature is made.

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SCIENCE AND THE BRITISH MEDICAL ASSOCIATION.

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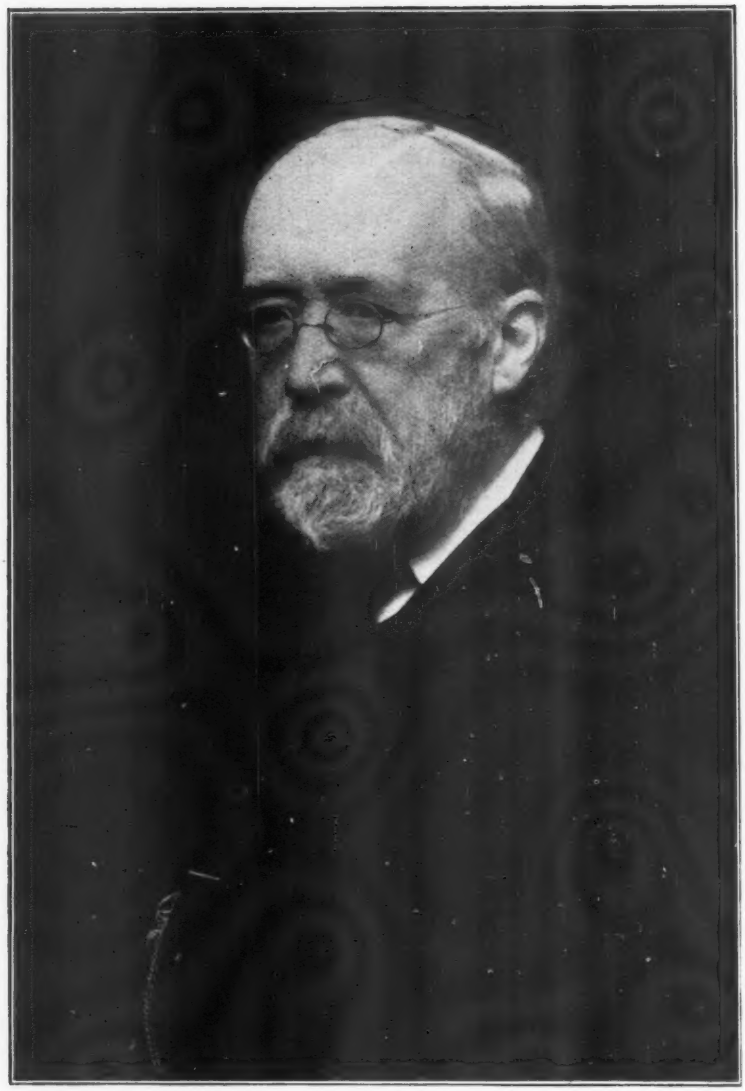

JOHN THOMSON.

Obiit 2, VII, 1926.

IN REBUS MEDICIS NEMO SAGACIOR.

IN REBUS HUMANIS NEMO HUMANIOR.

OBSERVATIONS ON THE RHEUMATIC NODULE.

BY

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Davaine[11] states that subcutaneous nodules were described by Sauvages in the second half of the eighteenth century, but that he did not associate these with rheumatism. It is said by Jaccoud[18] that Froriep was actually the first observer to do this in 1843. Hillier[15] in 1868, wrote copious notes on a boy aged 5, the son of a surgeon, who during the course of an attack of chorea, in which a systolic bruit conducted to the axilla developed, had numerous swellings about the head and joints. His final note is as follows: "This case is a remarkable one from the occurrence of the swellings on the head and near the knee and wrist. They must be regarded as due to rheumatic periostitis." Hillier's case appears to be the first of its type published in England.

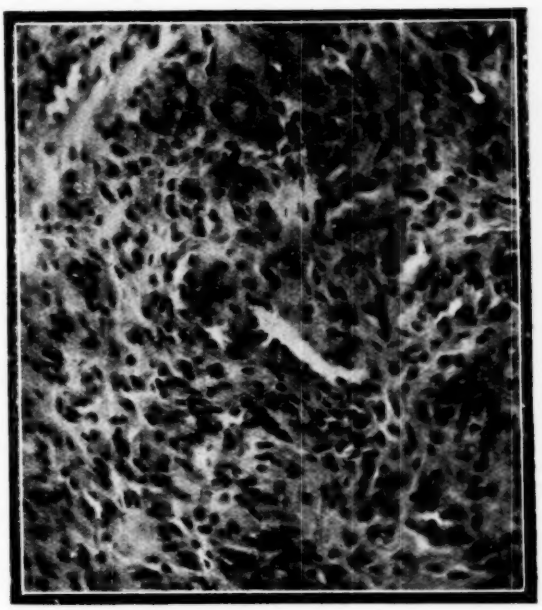
Jaccoud[18] in 1871, described rheumatic nodules, their situation and character, and stated that it might be necessary to locate them by palpation. He regarded them as an exceptional feature of rheumatic fever. In 1875, Meynet[19] described the case of a boy with nodules whom he first saw the previous year, and stated that they might be rheumatic or rheumatoid in nature, publishing this case as a curious one of articular rheumatism. In Gerhardt's book of children's diseases (1878) Rehn[24] describes tumours of the type previously referred to by Meynet, occurring in a girl of 10 with articular rheumatism. In 1881, Hirschsprung[16] described nodes in two children with cardiac disease. In one of these cases nodes from the region of the olecranon consisted of connective tissue with smooth, spindle-shaped and, here and there, larger nuclear cells; and also included copious and in part dilated vessels. There were multinucleated cells and areas with indications of necrobiosis. In 1881 also, Troisier and Brocq[25] recorded a case of rheumatic nodules which appeared in separate crops in an adult of 45. In this same year Barlow and Warner[2] gave their classical account of subcutaneous nodules, when they described 27 cases, the first being observed in 1875, with histological findings; and among other important conclusions considered "that such nodules belong strictly to the fibrous tissues and in nature are probably homologous with the inflammatory exudate which forms

the basis of a vegetation on a cardiac valve." In 1883, Angel Money[21] described an autopsy with subpericardial nodules which were "true homologues of subcutaneous nodules and ought to be called subpericardial nodules." Cavafy[4], examining a nodule, noted the marked proliferation of the endothelial cells of the vessels therein. Sir Dyce Duckworth[12] in 1883, was of opinion that several varieties of nodules existed. Mitchell[20], working in Osler's Clinic in 1888, was the first to describe a case of subcutaneous nodules in America. Cheadle[5], writing in 1889, considered that nodules were overlooked for three reasons; (*a*) they are rarely seen in adults from whom we take our conception of rheumatism; (*b*) they are not known of or looked for by physicians; and (*c*) they escape notice by their smallness.

So far, then, the node was generally understood in this country, and was beginning to be realised in America, as a fairly frequent and highly characteristic manifestation of the rheumatic infection of childhood. Further, several writers had dwelt on the essential similarity of these subcutaneous nodes to the inflamed areas of the serous membranes in active rheumatic carditis; an analogy carried further by the careful histological researches of Poynton and Still[23], and further again by a paper[9] in which one of us (C. F. C.) was able to show that the histological elements of which the subcutaneous node was composed were identical with those of the submiliary nodule (discovered by Geipel[14] in 1905 and by Aschoff in 1906[1]) in the rheumatic myocardium; and with the histological units of the changes seen in the rheumatic joint as well as in the serous membranes of the rheumatic heart. The constancy of the reaction of human tissues to rheumatic invasion was thus established, and the subcutaneous node shown to be merely the gross and palpable manifestation of a pathological process repeated in identical form, though on a smaller scale, in other parts of the body. The fact of its similarity to the submiliary myocardial nodule, now generally recognised as developing out of inflammatory changes in blood vessels, has also thrown a good deal of light on the origin of the subcutaneous node. Thus in histological notes on sections of a node made by one of us (C. F. C.), in 1912, the central core of fibrin that has been described by all observers of the structure of the node, is discussed: is it a true inflammatory exudate? or does it arise from coagulation within capillaries? or from rupture and extravasation of a larger vessel? The conclusion of the note is that the centre of the lesion is a thrombosis, around which is a zone of extraordinarily rich and exuberant proliferation of fibrous and endothelial cells; these last throwing off not only detached uninucleate cells, but also new capillary buds in great numbers, and forming, possibly as an early phase of this budding, the multinucleate cells that are so striking a feature of the rheumatic reaction. (Figs. 1, 2, 3, 4, 5.) These characters, the thrombotic centre and the endothelial periphery, stamp the node as a vascular lesion.

To these conceptions of the nature and significance of the rheumatic node little was added for some years, save that American physicians have added their testimony to the characteristic nature and prognostic significance

Fig. 1.



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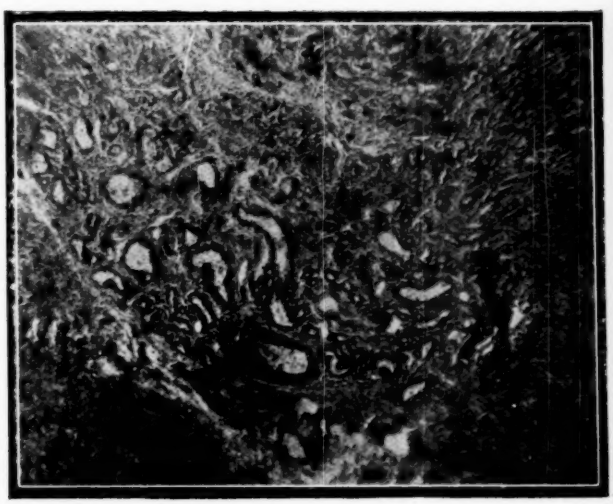

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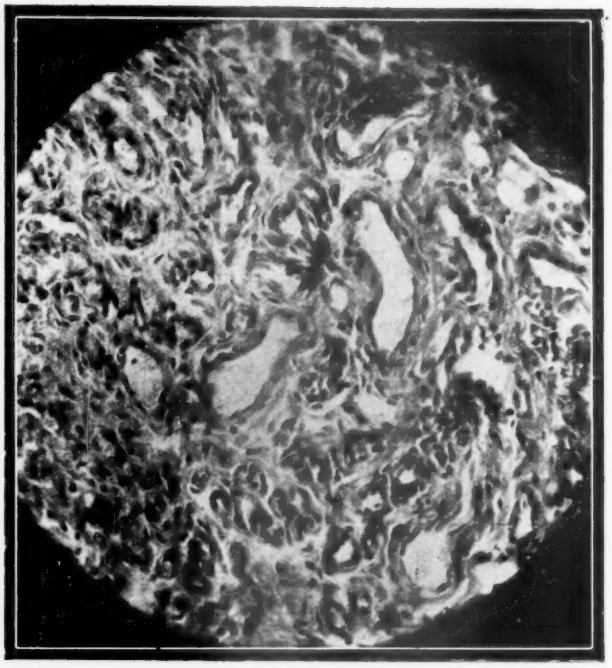

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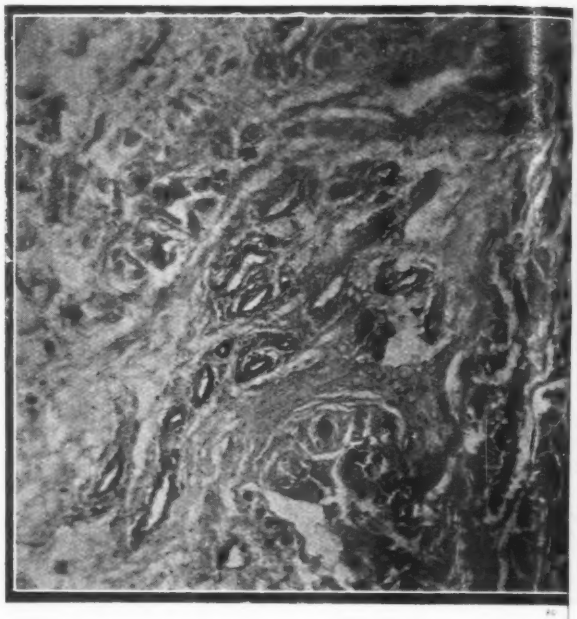

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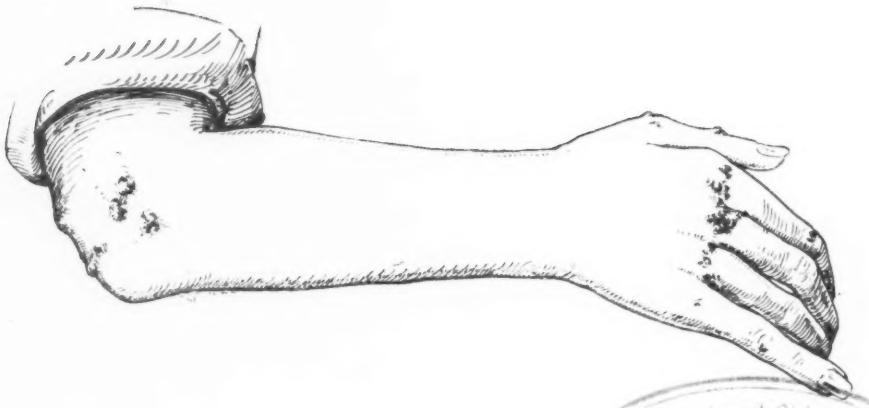

Fig. 6.

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of these lesions. In 1895, Futcher[13] from the Johns Hopkins Hospital, published a paper, with a good bibliography, dealing with subcutaneous nodes. Bronson and Carr[3] divided their series of cases into three groups—(*a*) Twelve children leaving hospital with apparently complete recovery after rheumatic fever, or at any rate without functional disability, only one of whom showed nodules; (*b*) nine with a definite carditis, but with the prospect of a fairly normal active life, three of whom had nodules; (*c*) seventeen with a crippling carditis and chronic cardiac failure, 13 of whom had nodules—of these 17, seven died, six of whom had nodules. The fourth paper from America of any importance is that by Wallace[26] in 1924, who stresses the not infrequent occurrence of nodules in Chicago. It must also be remarked that Poynton and Paine[22] were able to grow diplostreptococci from a rheumatic node, and that this has been repeated by Costa[10] and Irish[17].

All observations, then, bring us to this point: if there is any one lesion that is characteristic of rheumatic infection, and of severe infection at that, it is the rheumatic node. To this view we have to add some facts that tend to broaden the picture and at the same time to blur its outlines a little.

First, there is the fact already recorded by one of us (V. C.) that many children who present the picture of a smouldering rheumatic infection, yet without clinically demonstrable cardiac lesions, have small subcutaneous nodules which, when removed and examined under the microscope, show the same characteristic tissue reaction.. The fact that submiliary nodules occur in the myocardium in rheumatic carditis gave birth to the idea that there might be similar dissemination in other tissues, and the reproduction of the cardiac vegetations in the subcutaneous tissue as nodes pointed towards the likelihood of the same site being affected on a smaller scale by " pocket editions," comparable to the submiliary nodules. A very large number of children was therefore examined over a long period to make practice as perfect as might be, and when it was established that departures from the normal in respect of shotty thickenings and millet seed granules (" Granules " is the word suggested by Dr. Leonard Lees of Clifton) did occur, the investigation[6] of 100 consecutive out-patient children was undertaken. In 18 out of 23 who gave the usual history suggestive of rheumatic infection nodules were found, but none in the remaining 77 children. Some of these nodules were removed and sections were cut. (Figs. 7, 8, 9.) Subsequently a further investigation[7] was carried out by one of us (V. C.) in conjunction with Dr. R. E. Thomas and the fact established that these nodules are of very frequent occurrence in children, and the opinion was expressed that they were of diagnostic importance. It was later affirmed, moreover[8], that these nodules were in point of fact homologous with the submiliary cardiac nodules, and it is now suggested that these demonstrate the existence of a sub-palpable phase of infection. The outstanding feature of these nodules

Fig. 6 is a drawing of subcutaneous nodes by Miss D. Pillers from a patient under the care of (V. C.)

is not their rarity (once there has been sufficient practice in palpating them) but their extraordinary prevalence. Areas exposed to friction or lying over bony prominences are sites at which they can be most easily palpated, the ulnar borders and the vertebral spines in particular. In the former position a to-and-fro, in the latter a lighter rotatory movement of the examining finger has been found to be the best method of feeling nodules.

In what position then do we find ourselves if nodules are as frequent as growing pains? And what is their diagnostic value? The answer is found in a summary of our conception of the rheumatic complex as it occurs in childhood. It is the old parable of the seed and the soil. The seed is ever present in the alimentary tract; the soil is suitable either in virtue of heredity, or because of a lowering of immunity by many factors as yet improperly understood—for example, stress, damp, secondary infection and lack of sunlight. Subcutaneous nodules of the millet-seed order indicate that the barriers of immunity are being successfully assailed and that the result hangs in the balance: either the defence mechanism will recover from its partial dislocation or some added factor, such as a chill, will put it altogether out of gear.

No organisms other than streptococci of low-grade virulence are known to produce a like tissue response to that already described. It is this fact that confers on the subcutaneous nodule its diagnostic importance.

Second, we have severally examined nodes from patients whose other evidences of rheumatic infection were of a heterodox type. The following are selected from these :—

Case I (under the care of C. F. C.) was that of a youth of 22. At the age of 14, when he came under observation for the first time, he was pale and ill, and had his first attack of polyarthritis with a crop of typical nodes, but no evidence of carditis. This appeared shortly after and ran a severe course, leaving him a crippled heart. In spite of this he got into the Army in 1914 and managed to serve till 1917. Seen in 1920, he appeared to be suffering from endocarditis lenta, with hæmaturia, slight but persistent fever, œdema of the legs, and a few petechiæ. After various attempts to check the course of this had failed, he developed several crops of subcutaneous nodes, one of which over the right elbow (Fig. 10) was removed and sectioned. Soon after this he left hospital at his own request, and made an astonishing recovery, albeit with severe lesions of the aortic and mitral valves. He is still alive and at work. The sections of the node (Figs. 11, 12) showed that it had a kind of racemose arrangement. Its centre consisted of a fusion of several nodal masses and its periphery of two or three others which were separate from each other. Each of these masses had a fibrinous core surrounded by a zone of rich cell production, passing to an outer zone of new vessels and fibrous tissue. The new cells were fibroblasts, with an extraordinarily prolific endothelial reaction producing plasma cells, multinuclear cells, and new blood vessels in every stage of development. In one spot a giant cell of the type seen in tuberculosis was observed. In the fibrinous core of one of the peripheral masses, and less obviously in several parts of the central mass also, the matrix appeared to consist not only of fibrin but also of necrotic debris, in which there were many polymorphonuclear cells. The Gram stain failed to demonstrate cocci.

Case II. In this instance the node was removed from a patient with a rheumatoid type of arthritis, by Dr. Reginald Miller, who kindly handed it to us for examination. Here, again, the same structures were noted; a central fibrinous core, an intermediate

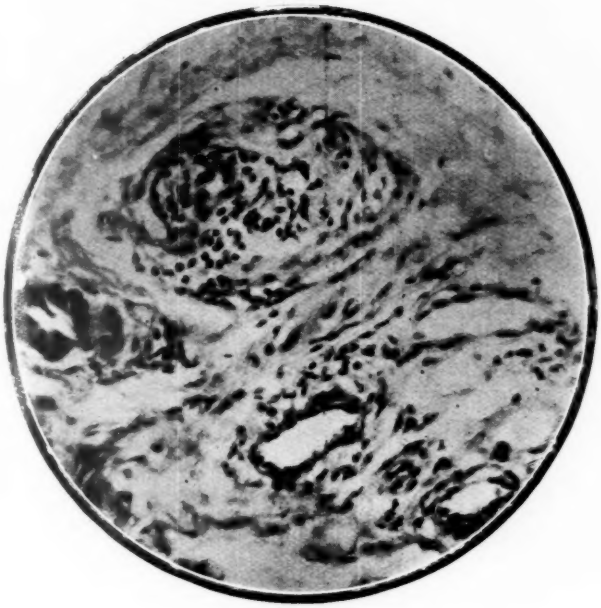
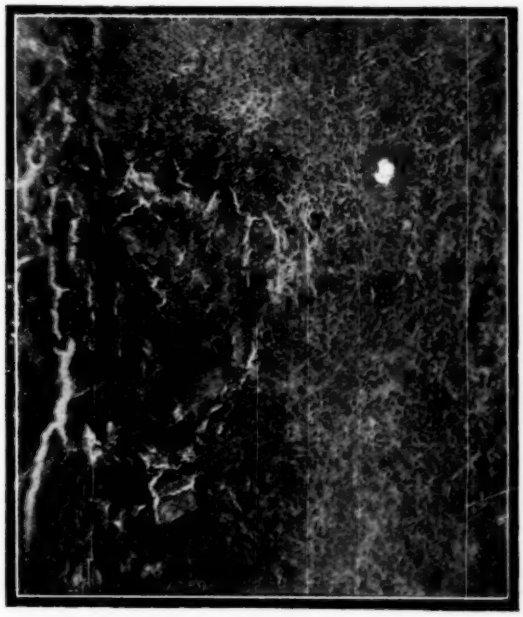


Fig. 8.

Fig. 9.

Fig. 10.



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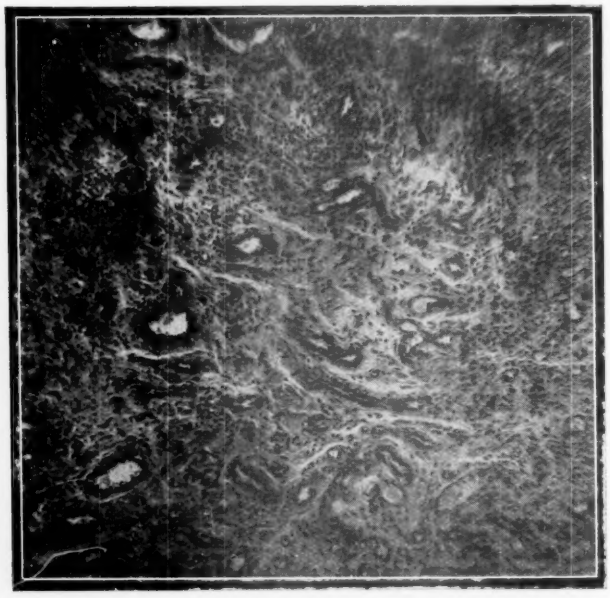

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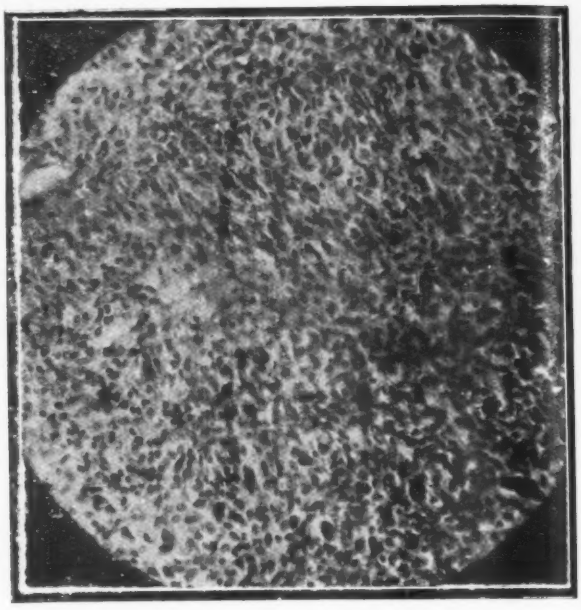

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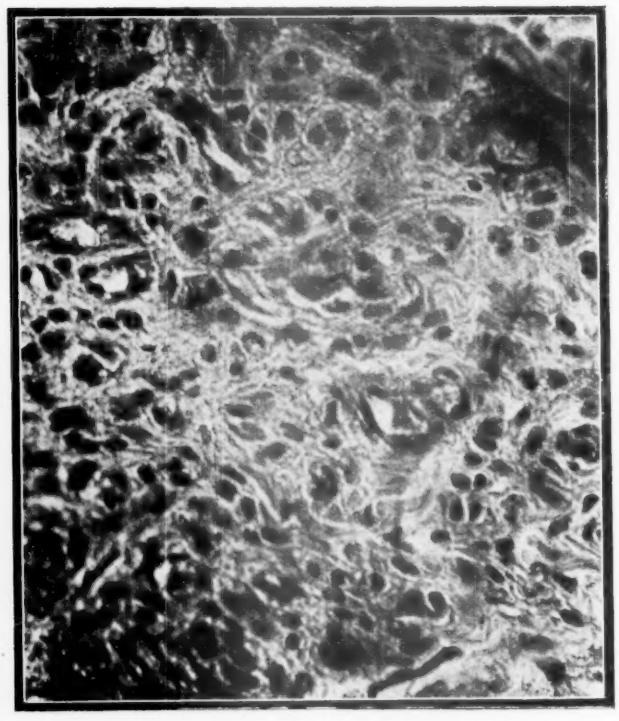

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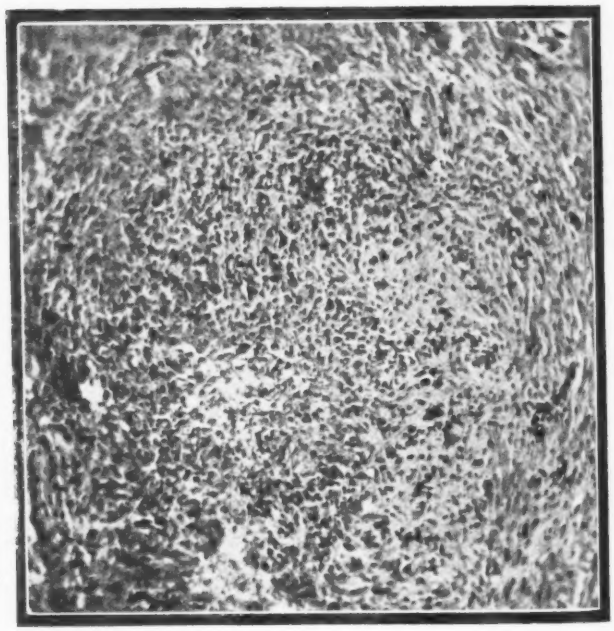

Fig. 15.

zone of exuberant formation of fibroblasts and endothelial cells, and an outer zone of newly-formed fibrous tissue and capillary blood vessels. (Fig. 13.)

Case III. This node was removed from a woman of 32 with a cardiac lesion of rheumatic type, a temporary enlargement of the spleen, polyarthritis with a tendency to chronicity in one knuckle, and subcutaneous nodes persisting after all fever and other acute symptoms had died down. For this specimen we are indebted to Dr. Ivor Davies of Cardiff.

Once more, the structure of this node (Fig. 14) is in all respects similar to that of rheumatism in childhood, and exhibits the same tendency to radiate in scattered masses, beyond the limits of the node itself, into the surrounding intermuscular planes of connective tissue.

Case IV was that of a girl of 13, under the care of one of us (V. C.). She gave no history of rheumatic fever or chorea, but had had pain and swelling in the knees and ankles nine months before. The swelling in the wrists, fingers, and ankles had persisted, and was rheumatoid in type. There was some enlargement of glands and the spleen was palpable. The heart was enlarged but without obvious valvular disease, there was persistent slight fever, bronchitis without tubercle bacilli in the sputum, and some root fibrosis. There was a gross secondary anæmia without leucocytosis. The subcutaneous nodes were very marked. One removed from the elbow, and sectioned, shows a fibrinous centre embraced within a ring of fibroblasts and endothelial cells in all stages of evolution. (Fig. 15.)

The similarity of these nodes drawn from varying sources is attested by the micro-photographs that accompany this article. We are greatly indebted for these to Dr. Geoffrey Hadfield, Pathologist to the Bristol General Hospital, who has given us invaluable help in this as well as in other departments of the present study.

Another point that serves to emphasise our thesis, namely, that the subcutaneous node is not quite so simple and plain an index of rheumatic infection as it seems at first sight to be, is the fact that nodes may occur more frequently in some years than in others. Thus, we have during the past three or four months seen in Bristol as many examples of the rheumatic node as we have seen in the preceding five years. This cannot be ascribed to more careful scrutiny; the nodes have been of such a size and prominence that they could not possibly have escaped notice. Neither is it wholly explained by an increased severity in the type of rheumatic infection. This appears to be partly responsible, but certainly not wholly so. Moreover, these particular nodes have disappeared very slowly, outlasting by weeks all other evidences of active infection.

One final observation we include because it serves to emphasise the fact that a rheumatic infection, as we understand it, is the outcome of many factors. We are not merely dealing with the impact of streptococci on a certain tissue and the reaction consequent on that impact. The form of this reaction, and, in all probability, the impact itself, are both of them the resultant of a number of forces. The observation to which we allude is that of a nodular area over the shin, taken from a patient with chronic ulcerative endocarditis; a lesion which was clinically a compromise between erythema nodosum and an Osler node. Sections of this area showed a central spot of acute polymorphonuclear leucocytosis with necrosis of the leucocytes,

amounting to pus formation; and some fibrinous deposit. Around this was a zone of fibroblastic and endothelial proliferation, infiltrated with many leucocytes. Organisms could not be demonstrated in these sections but streptococci were grown from another similar node.

In this case streptococci, probably of a kind akin to those associated with rheumatic infection, had been thrown into a subcutaneous blood vessel; yet the result was something different from a subcutaneous node. Possibly the node from our Case (I) represents a compromise between the typical node and the lesion just described. At all events it serves to prove that the way in which the organisms enter the tissues which they attack makes all the difference to the lesion that follows; a fact that has to be borne in mind when we are pondering on the difference between clinical rheumatic infection in man and experimental infection of animals with the same streptococci. So far as the clinical manifestations of rheumatic infection are concerned, what we are struck with is not their variability but—on the contrary—their uniformity. It is a wonderful thing that, time after time, the coincidence of certain essentials in the patient's inheritance and environment should enable a streptococcus, which has in all probability only just emerged from a saprophytic existence into a kind of " parvenu " pathogenicity, to inflict on the subcutaneous tissues an injury so constant in type and degree as it is proved to be by the reaction which it excites. We are much impressed by the close similarity to this reaction, of that seen in the nodes which we have described.

Summary.

(1) An account of the steps by which our knowledge of the subcutaneous node of rheumatic infection has advanced to its present position is offered.

(2) The occurrence of tiny granules in the subcutaneous tissues of the rheumatic child is described, and their significance discussed.

(3) Subcutaneous nodes from patients with rheumatoid arthritis, Still's disease, and endocarditis lenta, are described. They are shown to have been histologically identical with those of orthodox rheumatic infection.

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DESCRIPTION OF PLATES.

Figures 1, 2, and 3. Photomicrographs of a rheumatic node in its early stages, showing exuberant production of new fibrous and vascular tissue.

Figures 4 and 5. Photomicrographs illustrating later stages in the same process.

Figure 6. Drawing of subcutaneous nodes from a child with acute cardiac rheumatism.

Figures 7, 8, and 9. Photomicrographs from sections of the small subcutaneous granules described in the text.

Figure 10. Photograph of a subcutaneous node on the elbow in a case of endocarditis lenta.

Figures 11 and 12. Photomicrographs from sections of the same showing its essential similarity to the rheumatic node.

Figure 13. Photomicrograph of a subcutaneous node from a patient with rheumatoid arthritis; to show its fibroblastic nature.

Figure 14. Photomicrograph of a subcutaneous node from a case of atypical rheumatic infection, showing changes similar to those in Figs. 1-3.

Figure 15. Photomicrograph of a subcutaneous node from a case resembling Still's disease. The reaction is similar to that shown in Figs. 1-5.

CONGENITAL ABSENCE OF TIBIA.

BY

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I. Definition and Description
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This study was undertaken as an enquiry into the ætiology of congenital defects of bone, and into the indications for treatment in the particular case of partial or complete absence of the tibia. Although with regard to the former neither this nor any other of the recent investigations has succeeded in arriving at the whole truth, we hope that the ground has been cleared, several unsatisfactory hypotheses disproved, and the way opened up for the discovery of the ultimate cause in the course of our study. In addition, some light has been thrown on problems of embryology, comparative anatomy, and muscle physiology.

The material for this investigation is derived from a number of cases studied clinically and by radiographic examination, a series of dissections of specimens obtained from these cases, and an examination of the other specimens (except one recently described by Ollerenshaw[23]) in the Royal College of Surgeons Museum. A survey of all the available literature has also been made.

I.—Definition and General Description.

Congenital absence of the tibia is defined as " the absence at birth of the tibia in whole or in part, the lower limb being nevertheless present with its different segments well developed in their essential parts." This definition (modified from that of Launois and Küss[18]) excludes cases where the absence of the tibia is merely a part of a deformity such as absence of the

entire lower limb, or of deficiency of the distal segments of the limb, or of " congenital amputation " through the leg or thigh.

The deformity is one of the rarest of the congenital malformations, and certainly the most uncommon of those of the lower limb.

Hoffa's[13] statistics of 9,877 cases of congenital deformity of all sorts give 2,425 of the lower limbs, without mention of absence or defect of the tibia. The number of published cases now amounts to 102. Of these the first case described is stated by several writers to be that of Otto in 1841. Launois and Küss[18] in 1901, in a valuable paper, recorded 41 cases they had collected; and Nuzzi[22] in 1920, including these in his series, brought the number up to 81. The three cases of Clutton[7] (1896) and one each of Openshaw[24] and Muirhead Little[19] (1913) were, however, omitted from this list, as were also those of Boetticher (1904), Munro (1904), Spaunaus (1908), Davidson (1918), Tissier, and Broca (1914), since recorded by Bertaux[4] (1920) in publishing his own two cases. Further cases have recently been published by Rocher[26] (1920), Vallois and Roume[27] (1922) and Ollerenshaw[23] (three in 1925). The remaining three, those of Cautley[6] (1915), Elmslie[10] (1920) and Laming Evans's[11] second case (1923), are included in our own series, as, although they have been already reported clinically, they are now described anatomically for the first time. Finally to this list of 102 we add three more cases:—those of Thomas Bryant (1888), Laming Evans's first case (1915), and Fairbank (1924), which have not yet been published, bringing the total number up to 105.

Congenital absence of the tibia may be total or partial, unilateral or bilateral. Statistics given by different writers vary, and are not very reliable because many of the cases have been very imperfectly described; and, moreover, most of the descriptions have not been aided or confirmed by radiographic and anatomical examination. We agree with the conclusions of Bertaux[4], namely, that total absence is more frequent than partial, unilateral absence occurs more often than bilateral, and of the unilateral cases the defect is of the right limb more frequently than of the left. In none of these points, however, is the difference great. A noteworthy feature of the partial cases is that the defect is almost always of the distal end of the bone. Of the bilateral cases, there may be total absence on both sides, or total on one side and partial on the other.

With regard to sex there is a slight preponderance of males over females. In our own series there are three males, two females, and one with no record of the sex. Bertaux states that the affection is twice as common in males as in females; but our reading of the literature does not bear this out, and is in favour of the view above expressed.

The family history is usually negative for congenital abnormalities and other diseases. There are, however, a considerable number of instances of the occurrence of congenital defect of the tibia, or of other abnormalities, in near or remote relatives. In this connection Ollerenshaw's[23] recently published record of absence of the tibia in identical twin girls, the eleventh and twelfth children of a family otherwise normal, is interesting.

The nature of the birth is not stated in most cases. A few writers have noted deficiency of the liquor amnii or that labour was difficult. Others, however, have stated that birth was normal and pregnancy uneventful. Maternal injuries and impressions, and illness during pregnancy, have been noted in only a few instances.

Associated abnormalities are present very frequently. Launois and Küss[18] noted them in 24 out of their 41 collected cases. In five of the six cases in our series they were present. These abnormalities are not only confined to the limb where the tibia is absent, but may affect the upper limb, trunk or head. They are most common in the affected lower limb, occurring, for example, as congenital dislocation of the hip, ectro-, poly-, or syn-dactyly, or in the abnormalities of the bones and muscles of the thigh, leg, and foot, given in the anatomical description below. In the upper limb phocomelia, absence and partial defects of the forearm (of the radius most commonly), and of hand bones and fingers may occur; and with regard to the head and trunk, harelip and cleft palate, pseudo-hermaphroditism, cryptorchidism and hypospadias have all been observed in various cases.

It is rare to find any stigmata of fœtal disease in cases of congenital absence of the tibia. This statement is supported by the records of almost all the cases yet published. It is a striking fact, common perhaps to most congenital deformities, that, while possessing a gross defect such as that of absence of the tibia, the individual is usually otherwise perfectly healthy. These facts seem to throw considerable doubt on fœtal disease as a possible cause of the defect.

The subjects of this deformity are thus to be met with at any age, and it is worth while to observe their natural method of progression if untreated; this will be referred to again below.

II.—Clinical and Radiographic Features.

The characteristic signs of congenital absence of the tibia are:—

1. *Shortening of the leg.* This is invariably present to a greater or less extent, the degree depending largely upon the age of the patient when seen, since post-natal growth as well as pre-natal development is defective, and the affected leg becomes progressively shorter as compared with the normal and relatively to the other segments of the limb, as age advances. There is frequently also shortening of the thigh to a less extent. The shortening of the leg may be so marked that the leg appears as a mere appendage of the thigh. There is not necessarily wasting of the leg or thigh; they are in fact frequently well formed and plump.

2. *Flexion and adduction of the leg on the thigh.* These take place at the knee joint and their degree depends on whether the tibial defect is total or partial. In cases of total absence the flexion and adduction are well marked, constituting a gross deformity in which the inner borders of the leg and thigh may even be in apposition. Accompanying this are limitation of extension at the knee, and, usually, luxation of the head of the fibula upwards and backwards, so that it comes into contact with the postero-lateral aspect of the lateral femoral condyle, to which it is articulated by a well formed diarthrosis, or, less commonly, by a syndesmosis. When the tibia is only partially defective, and particularly when a considerable amount of

the proximal part of the bone is present, the flexion and adduction of the leg are less marked.

3. *Inversion of the foot on the leg.* This also is a constant feature. It occurs mainly at the ankle joint and is apt to be very marked, and is usually irreducible.

4. *Palpation.* This reveals that there is but one bone in the leg (in the case of total absence of the tibia) and that having the form and position of the fibula; where the absence is partial, the defect may be recognisable. The absence of the normal bony points, *e.g.*, the medial malleolus, is also determinable.

5. *Appearances on Radiographic Examination.* It is advisable that X-ray examination should be done in all cases, since it forms the most certain method of diagnosis, and the only sure way of determining whether or not the tibial defect is total or partial. It also gives valuable information of the state of osseous development of the other segments of the limb and of the pelvis.

6. *Minor features.* Certain other features, less constant and important, may be present. The fibula is often found to be not only shorter than normal, but also stouter and curved with convexity outwards, imparting a similar longitudinal curve to the leg. The prominence of the lateral malleolus is frequently a noticeable feature. The femoral condyles may be ill-formed or absent, as may be also the patella. Cutaneous dimples, grooves, constrictions and " scars " are often present; and abnormalities of the foot such as syndactyly, polydactyly, and ectrodactyly, or even more gross deformities are frequent occurrences.

When the tibial defect is partial, it is almost invariably the distal end which is absent. In one recorded case only (Parona[25]), quoted by Bertaux[4], has the proximal end been the absent portion. The proximal end may be a mere nodule, when it may not be palpable; it is, however, often larger, and is then apt to be conical in form with its distal end sharp-pointed and projecting forward beneath the skin of the leg. A puckering or mamillary elevation of the skin over this projection is not an uncommon feature.

Except in the uncommon cases of slight partial absence, the deformity resulting from the defect is so great as to make the natural method of progression impossible. The victims of this deformity are only able to move themselves either by jerking themselves forward on their buttocks with the aid of their hands, or by walking on their hands and knees. Some patients with unilateral defect learn to stand and walk upright with the aid of a crutch. One of the patients included in our series was able to walk well on her knees. The majority, however, are unable to move except in one of the ways described. In all cases of total defect, the leg is useless.

III.—Cases.

The series of cases here given includes three hitherto unpublished (Laming Evans's first case, Fairbank's and Bryant's cases); and five which have been already recorded elsewhere. The latter are included mainly for the sake of completeness, because in the anatomical section of the paper, descriptions are given for the first time of the specimens derived from them.

Case I. Laming Evans's first case (1915)—bilateral total absence of the tibia. G. T., male aged 3 weeks (Fig. 1). Royal National Orthopædic Hospital. Family history: Parents were healthy with no deformities in themselves or among their near relatives. There were ten previous children all without deformity, of whom eight are alive and well. Mother was aged 37 years. Pregnancy and birth were normal.

Fig. 1.

Both of the child's legs were flexed on the thighs at an angle of 80°. Scars were present over the prominence of the femoral condyles. The upper ends of the fibulæ were displaced backwards relatively to the femora; while the distal ends formed sharp-pointed prominences at the lowest points of the legs. Both tibiæ were completely absent. Each foot was displaced markedly inwards and upwards on the leg so as to lie along the medial side of the leg, which it overlapped at one point. The hallux was absent from both feet; and there were two toes only on the right foot. The right testicle was incompletely descended; the left hand had only three digits, the right hand two only with a deep cleft between them; and the right radius and ulna were abnormally short.

X-ray examination: In both legs one bone only is shown. This bone is well ossified and straight and almost certainly from its position relative to the foot, the fibula. There may be a slight doubt as to its identity because the proximal end lies not, as usual, to the lateral or postero-lateral aspect of, but in the middle line immediately below, the distal end of the femur.

No treatment was adopted at the time, and the child was not brought to hospital again.

Case II. Laming Evans's second case (1923)—left unilateral total absence of the tibia. B. B., male, aged one year and five months (Fig. 2). Royal National Orthopædic Hospital. Patient was the first child of young parents both without

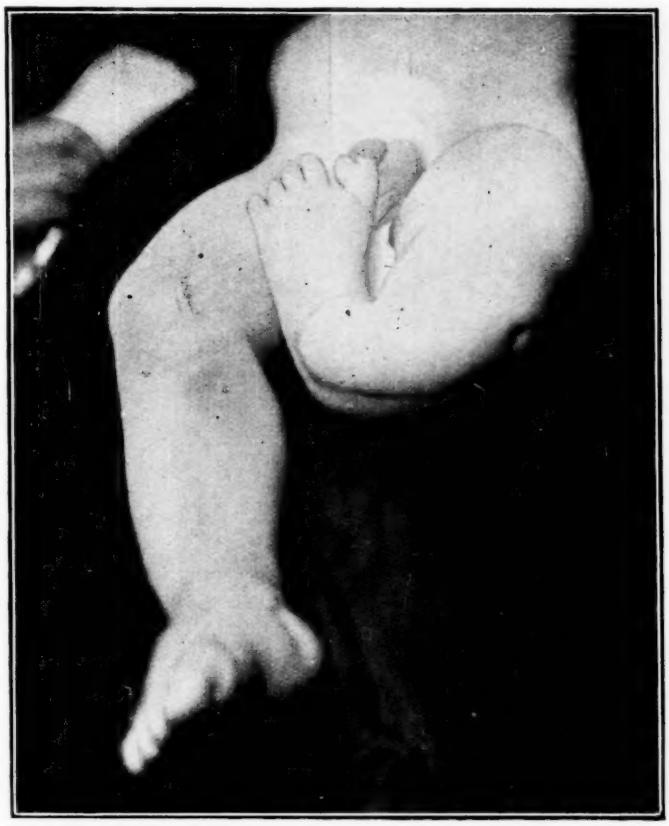

Fig. 2.

deformity and with no deformities in either of their families. Pregnancy and birth were normal. A second child had been born since without deformity.

The child was well developed and healthy. The left thigh was ½″ shorter and smaller in circumference than the right. The right patella was well developed; the left impalpable. The left leg was shorter than the right and was flexed upon the thigh. Flexion was complete, but extension was short by 45°. The upper end of the fibula was articulated with the upper part of the lateral femoral condyle. The fibula was palpable through its whole extent, was curved with convexity outwards, was thicker and one inch shorter than the right fibula. The lateral malleolus was unduly prominent. A deeply recessed dimple was present over the head of the fibula and was continued downwards over the outer aspect of the fibula as a linear scar-like depression.

The foot lay in complete supination along the inner border of the leg. The general conformation of the foot was normal, but the great toe was bifid in its ungual segment. The circulation was good and the limb not wasted. As far as one could tell sensation was normal. The left testicle lay in the high scrotal position; but there were no other abnormalities.

X-ray examination (Figs. 3 & 4). (i) The pubic segment of the os innominatum is still without sign of ossification (normally this centre appears in the fourth month

Fig. 3.

Fig. 4.

of intra-uterine life); (ii) the ossific centre for the head of the femur is absent on the left side; (iii) the left tibia is completely absent; (iv) ossification of the tarsus is normal; (v) the accessory toe lies on the medial side of the ungual phalanx of the hallux, and has two centres of ossification, thus resembling the four outer toes.

The treatment adopted was amputation at the knee joint. The specimen was dissected (*see* below).

Case III. R. C. Elmslie's case (1920)—bilateral total absence of the tibia. M. M., female, aged 13 years (Figs. 5 & 6). St. Bartholomew's Hospital. The tibia was totally absent in both lower limbs producing gross deformity, the legs being flexed to a right angle and displaced outwards and backwards on the thighs, and externally rotated. The patellæ were present and the femoral condyles well developed. The heads of the fibulæ were large, and articulated with the outer side of the lateral femoral condyles. Severe talipes equino-varus was present on both sides. The second toe was absent from the right foot, a deep cleft existing in its place. The hallux was missing from the left foot. The child walked well on her knees.

X-ray examination (Figs. 7 & 8). (i) Total absence of the tibiæ; (ii) both patellæ present and well formed; (iii) luxation of the heads of the fibulæ to the postero-lateral aspect of the distal ends of the femora; (iv) absence of the left hallux and all but the base of the first left metatarsal, and in the right foot absence of the second toe and fusion of the first and second phalanges of the third and fourth toes.

Fig. 5.

Fig. 6.

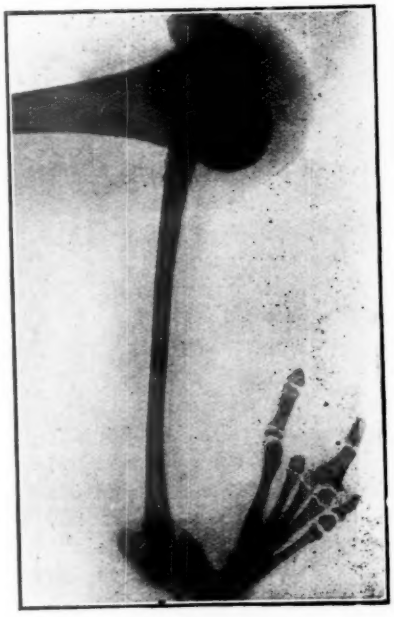

Fig. 7.

Fig. 8.

Amputation at the knee joint on both sides was performed and peg-legs subsequently fitted. A note eighteen months later stated that the child was walking well. (For description of the specimens *see* below.)

Case IV. H. A. T. Fairbank's case (1924)—right unilateral absence of the tibia. J. R., male, aged two years (Fig. 9). Hospital for Sick Children. The right tibia was totally absent. The patella was palpable and the femoral condyles well developed. The head of the fibula articulated with the lateral condyle. The foot was in extreme varus; only one toe and two metatarsals were present, and, of the tarsus, the calcaneus was alone determinable. Left talipes varus was also present, with fusion of the second and third toes, and absence of the first, fourth and fifth metartarsals, and absence of the navicular. The right hand showed the "lobster claw" deformity with associated deficiency of the carpus. The left hand bore only one digit (a thumb) and the left carpus was also deficient.

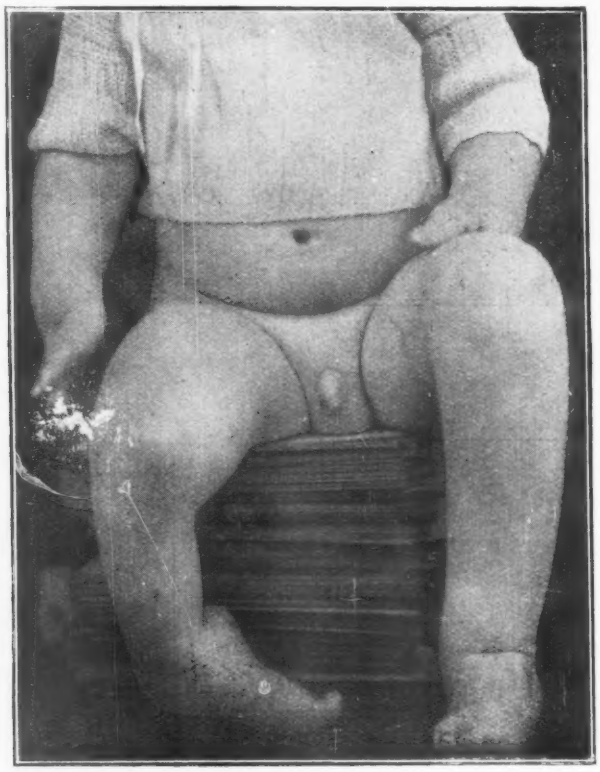

Fig. 9.

X-ray examination (Fig. 10). (i) In the right lower limb, the hip joint is normal, the tibia totally absent, the head of the fibula luxated to the postero-lateral aspect of the distal end of the femur, the calcaneus and cuboid present; (ii) in the left foot, the calcaneus, cuboid, talus, two metatarsals, and two digits are shown, and the lower epiphysis of the tibia appears to be in two portions; (iii) in the right hand, the outer digits consist of two phalanges and one metacarpal, the carpal region casts no shadow, and the lower end of the radius and ulna are normal; (iv) in the left hand the digit consists of three bones, two phalanges and one metacarpal, and there is no shadow in the carpal region; (v) the pelvis is normal.

Amputation of the right leg through the knee joint was carried out, the patella being left in the flap. (For dissection of specimen *see* below.)

Fig. 10.

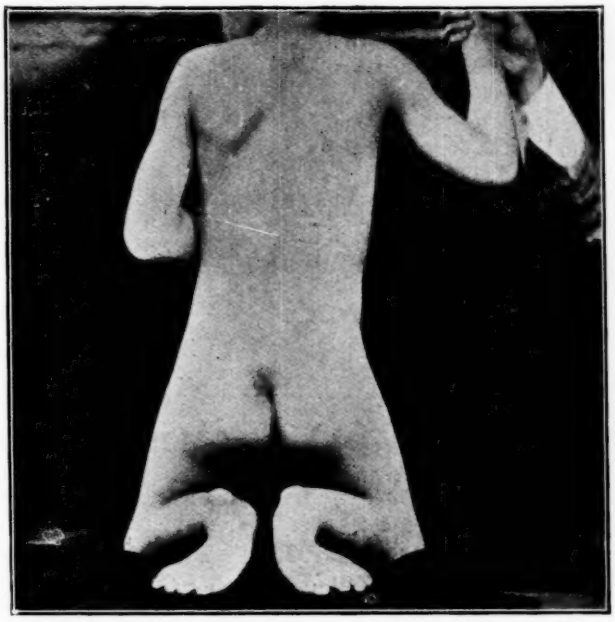

Fig. 11.

Case V. E. Cautley's case (1915)—right unilateral partial absence of the tibia. Female, died æt six months, from " zymotic enteritis," weighing 6½ lbs. at death. The child was the fifth of a family in which there had been no member with deformity. The right lower limb was shorter than the left, and was inwardly curved. The foot had seven toes, the accessory digits lying to the inner side of the hallux and being identical with the normal second and third toes. The hallux was short, and the second and third toes were closely united almost to the proximal end of the terminal phalanges. The fibula was thought at the time to be absent and the tibia to be very much curved; but dissection (*see* below) has shown the fibula to be present and the tibia defective. The left foot closely resembled the right in appearance, presenting similar extra toes. There was also webbing of the extra toes and the normal second and third toes.

Case VI. Thos. Bryant's case (1888)—total absence of the right tibia.

No clinical record is available of this case which is reported for the first time here. A description of the dissected specimen is given below.

Case VII. Clutton's second case (1896)—bilateral total absence of the tibia. Female, aged eight years, in whose family there were no deformities. (Fig. 11). The tibia was totally absent in both limbs. The femoral condyles were under-developed, the femoral shafts ending in rounded knobs. The proximal end of each fibula was attached to the outer side of the distal end of the femur. The left great toe was very small, with associated deficiency of the tarsus and metatarsus on the inner side. Four right toes only were present; and there was also a deficiency of the inner part of the tarsus and metatarsus.

(*Note.*—These were clinical observations only, not confirmed by X-ray examination.)

Amputation at the knee was performed in both limbs. At operation it was noted that the patellæ and the ligamenta patellæ were absent, and that there was no joint

cavity on either side, the ends of the femora and fibulæ being cartilaginous and bound together by fibrous tissue. The specimen has been dissected and the description is given below.

Case VIII. Bland-Sutton's case (1892)—left unilateral total absence of the tibia. Female, aged 18 years, healthy. The left leg was relatively short. The tibia was totally absent, and the fibula short, but otherwise well developed. The distal end of the fibula articulated with the talus; and the foot was in an extreme equino-varus position.

Amputation through the knee was adopted. A description of the macerated specimen is given below.

IV.—Diagnosis.

The diagnosis is rarely difficult. The deformity, with its three features of shortening of the leg, flexion and adduction at the knee, and marked varus of the foot, is, except in cases of slight partial defect, a gross one and pathognomonic in itself. Palpation reveals that one bone alone is in the leg, or that the tibia is partially defective; and X-ray examination makes the diagnosis certain. Difficulty has been reported in deciding whether the bone felt in the leg is the fibula or the tibia. This difficulty is strongly insisted on by some authors, who point out that it is increased by the tendency for modifications to occur in the size and shape of the fibula when the tibia is absent, and *vice versa*. One of the cases in our series was first shown at a clinical meeting as a case of absence of the fibula, and on subsequent dissection has been proved to be one of partial defect of the tibia. Ordinarily, however, there should be no difficulty; when the fibula is absent the foot is everted and the knee joint is well formed, though there may be flexion at the knee. Shortening of the leg is common to both affections.

Where the distal third only of the tibia is deficient the resulting deformity might be mistaken on a cursory examination for the ordinary congenital talipes equino-varus of a severe kind, but the absence on palpation of the medial malleolus and the radiographic examination easily determine the diagnosis.

V.—Anatomical Description.

1. *Laming Evans's case* (1924)—R.C.S. Museum, Teratological Series No. 439.52.

The skin is normal and bears no scars. Over the outer aspect of the head of the fibula is a dimple, from which a groove runs downwards on the outer side of the leg in the line of the fibula to the lateral malleolus. (Microscopic examination of the skin of the groove shows no scar, but diminution in the thickness of the basal layers of the epidermis.) The nails are fully grown and the skin is hairless. The superfical fascia is abundant. No bursæ are present. The deep fascia is very thin and the special bands poorly developed: the plantar aponeurosis is ill defined and the ligamenta transversum cruris and laciniatum indistinguishable; but the ligamentum cruciatum cruris and the peroneal retinacula are clearly marked.

Muscles.—(Figs. 12 & 13). The quadriceps femoris tendon, thin and expanded, blends with the front of the capsule of the knee joint. The tendons of no other thigh muscles are present, except one on the medial side, which, from its insertion into the fibro-cartilaginous mass at the proximal end of the representative of the tibia, is presumably that of semimembranosus. All the muscles of the leg and foot are present;

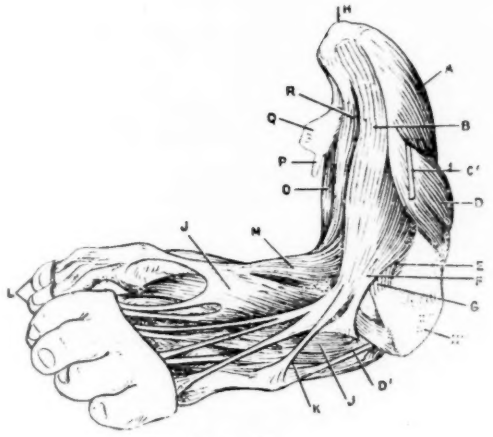

Fig. 12.

Antero-lateral aspect of leg and dorsum of the foot: A—Peroneus Longus; B—Extensor Digitorum Longus; C¹—Superficial Peroneal Nerve; D—Peroneus Brevis; D¹—Peroneus Brevis tendon; E—Interosseus Membrane; F—Peroneo-tarsus Anterior; G—Distal end of Representative of Tibia; H—Proximal end of Fibula; H¹—Lateral Malleolus; J—Extensor Digitorum Brevis; K—Peroneus Tertius; L—Hallux; M—Extensor Hallucis Longus; O—Flexor Digitorum Longus; P—Semimembranosus tendon; Q—Fibro-Cartilaginous proximal end of Tibial representative; R—Tibialis Anterior.

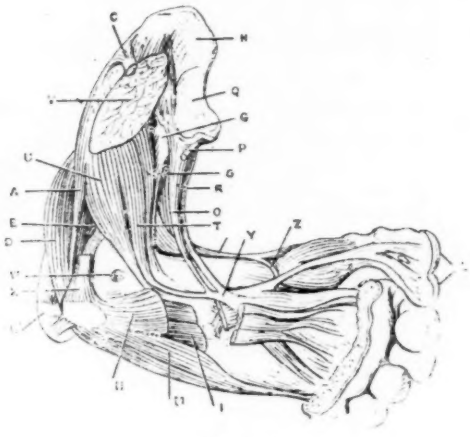

Fig. 13.

Postero-medial aspect of leg and sole of the foot: A—Peroneus Longus; C—Common Peroneal Nerve; D—Peroneus Brevis; E—Interosseus Membrane; G—Representative of Tibia; H—Proximal articular surface of Fibula; H¹—Lateral Malleolus; I Quadratus Plantæ; L—Hallux; M—Abductor Digiti Quinti Proprius; N—Flexor Digitorum Brevis; O—Flexor Digitorum Longus; P—Semimembranosus tendon; Q—Fibro-Cartilaginous proximal end of Tibial representative; R—Tibialis Anterior; S—Tibialis Posterior; T—Flexor Hallucis Longus; U—Peroneo-Tarsus Posterior; V—Cut surface of Soleus; W—Sinus Tarsi; X—Tendo Calcaneus; Y Common tendon; Z—Abnormal tendon giving origin to Abductor Hallucis and Flexor Hallucis Brevis.

but their arrangement is abnormal, and there are also present several muscles which have no place in the normal limb. Arising by a continuous fleshy origin from the upper four-fifths of the anterior border of the fibula is a muscle which divides in front of the ankle into three tendons running to the lateral three toes, a tendon to the base of the fifth metatarsal, and a fleshy remainder which is inserted into the dorsal surface of the calcaneus. This muscle therefore represents a part of extensor digitorum longus, peroneus tertius, and a peroneo-tarsus. The tendon of extensor hallucis longus is joined on the lateral side by the fibres of extensor digitorum brevis and is inserted by two slips into the two distal phalanges of the great toe. Extensor digitorum brevis is very large. The medial fibres join the tendon of extensor hallucis longus; in addition there are four tendons, two to the second toe and one each to the third and fourth toes. Abductor hallucis is small and has an abnormal origin from the side of a slender tendon which springs from the medial side of the tendon of extensor hallucis longus on the dorsum of the foot. This tendon, traced round the medial border of the foot, is found to proceed from a fleshy belly lying in the sole deep to the extensor tendons, superficial to the oblique head, and arising from the fascia covering the transverse head of adductor hallucis and the interossei. Flexor hallucis brevis also partly arises from the tendon; but the rest of its origin is normal. Peroneus longus and brevis are large relatively to the other muscles of the limb. Their attachments are normal.

On the posterior aspect of the limb the arrangement of the muscles is more abnormal and the value of each more difficult to determine. The tendons of three muscles unite, as in the specimen described by Symington and Craig(8) in the sole to form a common tendon from which arise five tendons, one to each of the toes. Quadratus plantæ joins the deep surface of the tendon and the four lumbricals arise between all five tendons. Of the three muscles entering into this arrangement one arises from the fibro-cartilaginous upper end of the tibial representative, from the anterior aspect of the interosseus membrane, and from the upper fourth of the anterior part of the medial surface of the fibula, and therefore appears to be tibialis anterior; the second muscle also derives

origin from the cartilaginous mass, and since the fibres it contributes to the common tendon go mainly to the tendons of the second, third and fourth toes it is presumably flexor digitorum longus; the third muscle is flexor hallucis longus, since it springs from the posterior surface of the fibula and its fibres are traceable into the slip to the great toe. The tibialis anterior element of the common tendon is given mainly to the tendon to the fifth toe. Tibialis posterior is recognisable in a muscle arising from the fibula posterior to the attachment of the interosseus membrane, and from the membrane itself, and inserted into the medial aspect of the fused talo-calcaneus. A peroneo-tarsus posterior is present, arising from the posterior surface of the fibula and inserted by tendon into the plantar surface of calcaneus deep to quadratus plantæ. Triceps suræ is present with normal attachments. Plantaris and popliteus are absent. The muscles of the foot not hitherto mentioned are present and normal.

Blood Vessels and Nerves.—These are healthy and have practically a normal arrangement.

Bones.—(Fig. 14). The patella is represented by a small flattened nodule of cartilage (confirmed by microscopal examination) in the anterior part of the capsule of the

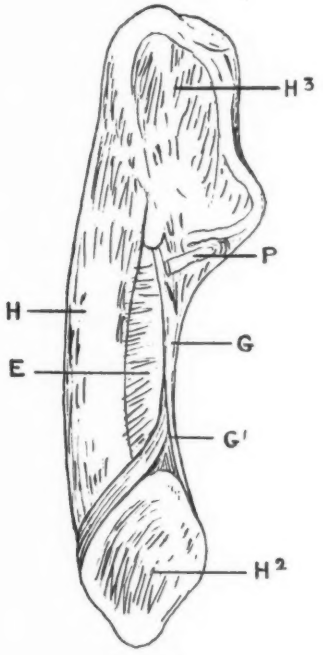

Fig. 14.

Diagram of form and attachments of Representative of Tibia: E—Interrosseus Membrane; G—Tendinous portion of representative; G1—Bifurcated distal end; H—Fibula; H2—Distal Articular surface of Fibula; H3—Proximal articular surface of Fibula; P—Semimembranosus tendon.

knee joint. (The distal end of the femur, seen at the operation of removal of the limb, had no condyles and no intercondylar notch, but was a rounded knob covered with articular cartilage on all aspects except the medial.) The fibula is short and stout, slightly curved longitudinally, with the convexity laterally. The shape, surfaces, and borders differ little from the normal. The proximal articular surface is on the medial aspect of the head and upper end of the shaft, thus extending across the line of the proximal epiphysis. (As seen at operation this surface lay in contact with the articular surface of the distal end of the femur.) The distal articular surface on the medial aspect of the distal end enters into the formation of the ankle joint, and is apposed to the articular surface on the lateral aspect of the talus.

The tibia is represented by a strong cord-like tendinous structure attached to the fibula by a well-formed interossoeus membrane. It contains no bony element; but at the proximal end it expands into an amorphous mass of dense fibrous tissue and cartilage, the proximal surface of which enters into the formation of the knee joint, while on the distal, medial and lateral aspects muscles are attached as described above. The deep aspect of the mass is attached to the medial surface of the fibula immediately distal to the proximal articular surface. The distal end of the tendinous structure is divided into two strong bands attached to the anterior and posterior borders of the distal end of the fibula, and entering into the formation of the ankle joint. The interossoeus membrane extends proximally as far as the distal part of the fibro-cartilaginous mass, and ends in a free upper margin over which passes the anterior tibial artery. The talus and calcaneus are fused; but each is well formed and the sinus tarsi is present. The other bones of the tarsus and the metatarsus are present and normal. The proximal phalanx of the hallux articulates distally with two nail-bearing elements: the lateral consists of a single phalanx, the medial of two phalanges.

Joints.—The joint representing the knee is formed by the distal end of the femur, the proximal end of the fibula, and the proximal end of the tibial representative. The articular surfaces and the relative positions of the parts entering into the joint have been described above. The capsule is well formed, attached below to the border of the amorphous mass described, and, elsewhere, close to the margins of the articular surfaces. The thin expansion of the quadriceps tendon forms the anterior part of the capsule. The menisci and ligamenta cruciata are absent. The ankle joint is formed between the upper surface of the talus, the distal end of the fibula, and the bifurcated distal end of the representative of the tibia. The capsule is thin and shows no specialised bands. The other joints of the foot are normal.

Summary.

1. The dimple in the skin over the head of the fibula with the continuing groove over the whole length of the outer border of the leg, the depressions not being due to scarring.
2. Absence of certain muscles, both of the thigh and leg.
3. Extensor digitorum longus which is partly a long extensor of the toes, but contains also peroneus tertius and peroneo-tarsus elements.
4. Origin of abductor hallucis indirectly from extensor hallucis longus.
5. Union of tendons of tibialis anterior, flexor digitorum longus and flexor hallucis longus to form a common tendon from which arise the flexor tendons for the five toes.
6. The presence of a peroneo-tarsus posterior.
7. The presence of a small patella.
8. The absence of the femoral condyles and intercondyloid fossa.
9. The short hypertrophied fibula slightly outwardly curved, articulating with the distal end of the femur by an articular surface extending across the proximal epiphyscal line.
10. The representation of the tibia by a tendinous cord, ending proximally in an amorphous fibro-cartilaginous mass, and distally bifurcating to form the upper wall of the ankle joint.
11. The fusion of the talus and calcaneus.
12. The accessory hallux.
13. The absence of the menisci and cruciate ligaments from the knee joint, which is formed between the distal end of the femur, proximal end of the fibula, and the fibro-cartilaginous representative of the proximal end of the tibia.

2. *Elmslie's case* (1923)—R.C.S. Museum Teratological Series No. 439.5.

The specimen has been fully dissected to show the arrangement of the muscles and articulations.

Muscles.—No tendons of muscles of the thigh normally inserted around the knee are present in the specimen.

On the posterior aspect of the leg, the popliteus is absent. Plantaris, lateral head of gastrocnemius, and soleus arise from the head of the fibula. Plantaris tendon joins tendo calcaneus, which has a normal insertion. Tibialis posterior arises from the head of the fibula immediately below and in front of the upper articular surface, and is inserted into the upper surface of the fused talus and calcaneus. Flexor digitorum longus is double. One muscle arises in common with tibialis posterior; its tendon breaks into three slips—the largest divides into tendons for the fourth and fifth toes, one is inserted into the talo-calcaneus in front of tibialis posterior, and one joins that part of the tendon of flexor digitorum brevis which unites with the second flexor digitorum longus. The latter arises partly in common with extensor digitorum longus from the head of the fibula and partly with extensor hallucis longus from a shaft of the fibula; the tendon, after giving off a slip attached to the navicular, is joined by the medial tendon of flexor digitorum brevis, and then breaks into two tendons, one of which goes to the third toe, and the other is inserted into the head of the second metatarsal. (*Note*.—The second toe is absent.)

The flexor and extensor hallucis longus arise together from the shaft of the fibula. From a single fleshy belly arise in the foot two tendons, one of which joins flexor hallucis brevis, while the other, after receiving laterally a tendon from extensor digitorum brevis, is inserted into the dorsal surface of the great toe.

Anterior Muscles.—Of the other muscles of this group extensor digitorum longus, with origin as described above, gives off a tendon to each of the lateral three toes and to the head of the first metatarsal; the peroneus tertius and tibialis anterior are absent. An abnormal muscle similar in position and attachments to that found in Fairbank's specimen, and so to be designated a peroneus, is present. It is a large musculo-tendinous mass attached to the front of the upper two-thirds of the shaft of the fibula and with no other attachment beyond the fibula. (Microscopic examination shows that the muscle fibres are abnormally large and not degenerated in any way.)

Peronei longus and brevis are normal. In the foot abductor hallucis is absent, and the tendon of flexor hallucis longus joins the short flexor as described above. Flexor digitorum brevis has two tendons: the lateral is joined by the very small quadratus plantæ, and itself joins the slip of flexor digitorum longus to the fourth toe; the medial, re-inforced by a slip from the lateral flexor digitorum longus, joins the tendon of the medial flexor of the toes.

Bones.—The tibia is completely absent and has no representative. The fibula is slightly hypertrophied, but is not bowed. On the postero-lateral aspect of the head is an articular surface for the femur. The distal end articulates with the talus. The talus and calcaneus are both malformed and are fused. The other bones of the tarsus and all the metatarsals are present; but the second toe is absent, and there is fusion of the proximal and middle phalanges of the third and fourth toes.

Articulations.—The knee joint is well-formed between the distal end of the femur and the head of the fibula. The articulations between the distal end of the fibula and the talus and those of the foot are normal.

Summary.

1. The absence of the tendons of the thigh muscles and of certain muscles, particularly peroneus tertius, tibialis anterior and abductor hallucis, of the leg and foot.
2. The duplication and partly abnormal insertion of flexor digitorum longus.
3. The origin of flexor and extensor hallucis longus tendons from a common muscle belly.
4. The presence of a peroneus identical in position and attachments and microscopic appearances to that of Fairbank's specimen.
5. The absence of any representative of the tibia.
6. The practically normal fibula.
7. The knee joints formed between the proximal end of the fibula and the distal end of the femur with absence of menisci and cruciate ligaments.
8. The malformation and fusion of talus and calcaneus.
9. The absence of the second toe and synostosis of the phalanges of the third and fourth toes.

3. *Fairbank's case* (1924)—R.C.S. Museum Teratological Series No. 439.6.

The skin, subcutaneous tissue and deep fascia had been removed before this examination was made.

Muscles.—(Fig. 15). The leg was amputated through the knee joint. The tendons of none of the thigh muscles, with the exception of the quadriceps extensor, are present.

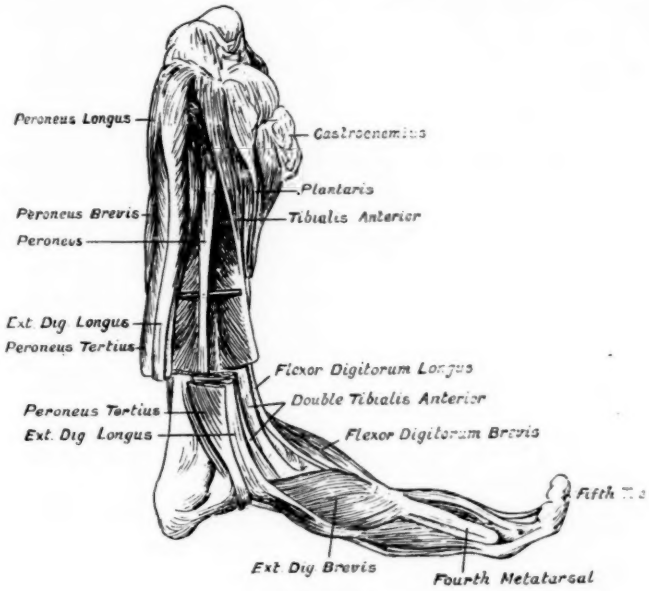

Fig. 15.

Of the posterior muscles of the leg, popliteus and flexor hallucis longus are absent. The medial head of the gastrocnemius arises partly from the femur, partly from the medial side of the head of the fibula. The lateral head arises from the lateral side, and soleus from the posterior aspect of the head of the fibula. The tendo calcaneus is inserted as normally into the calcaneus. Plantaris arises, in conjunction with the medial head of gastrocnemius and tibialis anterior, from the medial side of the head of the fibula, and is inserted into the calcaneus alongside tendo calcaneus. Tibialis posterior, arising from the upper half of the posterior surface of the fibula, divides into a tendinous and a fleshy slip, which are inserted, the latter behind the former, into the upper surface of the calcaneus. Flexor digitorum longus, arising from the middle of the shaft of the fibula, has only one tendon, which is joined on the dorsum of the foot by extensor digitorum brevis, and is ultimately inserted into the terminal phalanx of the toe.

In the sole of the foot abductor and adductor hallucis, flexor hallucis brevis and quadratus plantæ are absent. One lumbrical only is present, arising from the inner side of the tendon of flexor digitorum longus. Flexor digitorum brevis and abductor digiti quinti have a normal origin; but the former is inserted partly by a tendon into the toe and partly by a separate musculo-tendinous slip into the lateral side of extensor digitorum brevis, superficial to the attachments of flexor digitorum longus. Two plantar and one dorsal interossei are present.

Peroneus longus is inserted into the plantar aspect of the bases of both the metatarsals present in the foot. Peroneus brevis gives rise to two tendons: the posterior is inserted into the base of the lateral metatarsal, and, by a continuing slip, into the proximal phalanx of the toe; the anterior is continuous with the tendon of a muscle (presumably peroneus tertius), arising from the lateral aspect of the fibula, immediately in front of the peronei longus and brevis. Thus is formed between two muscle bellies a strong tendinous loop, which lies in a groove on the plantar surface of the calcaneus beneath the articulation of that bone with the fibula.

On the anterior aspect of the limb and dorsum of the foot are recognisable: (i) A muscle arising from the fibula, in front of the muscles just described, which is probably an extensor digitorum longus. It is inserted by a tendinous expansion into the calcaneus; but definite strands can be traced forward through the fascia covering extensor digitorum brevis to join the tendons of that muscle which go to the toe and to the base of the medial of the two metatarsals. (ii) A double tibialis anterior. One arises from the whole length of the fibula in front of extensor digitorum longus and is inserted into the medial border of the calcaneus. The other takes origin by two bellies from the proximal end and upper part of the shaft of the fibula, and is inserted into the calcaneus immediately in front of the former muscle. (iii) A muscle which arises from the upper end of the fibula, has a very short belly and a relatively very long tendon, which passes distally in close contact with the bone to be inserted into the distal end of the fibula. This muscle probably corresponds to the peroneus described in other specimens. (A microscopic examination of the muscle fibres shows them to be larger than normal and without signs of degeneration.) (iv) An extensor digitorum brevis arising by two bellies from the calcaneus and inserted into (*a*) the side of flexor digitorum longus tendon, (*b*) the side of the tendon of flexor digitorum brevis to the head of the medial metatarsal, (*c*) the distal phalanx, (*d*) the proximal phalanx of the toe. The last is joined by a tendinous slip from extensor digitorum longus. Extensor hallucis longus is absent.

Arteries and Nerves.—Both are large and the general arrangement of each is normal. The anterior tibial artery ends in front of the distal end of the fibula. The posterior tibial artery runs in the foot in the situation of the lateral plantar artery. There is no medial plantar artery. The tibial nerve divides into medial and lateral plantar nerves; but the medial gives no muscular branches.

Bones.—The tibia is entirely absent and there are neither cartilaginous nodules nor a fibrous strand to denote its position. The fibula is slightly thicker than normally. It is straight. The upper extremity bears on the postero-superior aspect an articular facet for the distal end of the femur. The lower end forms the lowest part of the limb and has an articular surface on the postero-lateral aspect for the calcaneus. There is no sign of interosseus membrane.

In the tarsus, the talus, navicular and cuneiforms are absent. The calcaneus is malformed and almost inverted, so that the tuberosity is uppermost and lateral to the fibular articular surface, which is on the proximal part of the upper surface. The cuboid articulates with the calcaneus and supports the only two metatarsals present, which are presumably the fourth and fifth. In support of this are the characteristic shape and the muscular attachments of the lateral of the two bones. One toe, comprised of three phalanges, alone is present. It articulates with the lateral metatarsal and is therefore the fifth toe.

Articulations.—The knee joint is formed between the distal end of the femur and the proximal end of the fibula. The articular surfaces are covered with articular cartilage and the joint possesses a well-formed capsule. The ankle joint is well formed between the distal end of the fibula and the calcaneus; slight antero-posterior gliding movements only are allowed. Well-formed joints exist between the other bones of the foot.

(Operation note by Mr. H. A. T. Fairbank: There was a definite large joint cavity in the knee with the fibula articulating over a considerable area of the outer condyle. The patella was present. The femoral condyles were well formed.)

Summary.

1. The total absence of the tibia and of all the structures of the inner segment of the foot, *viz.*, the talus, navicular, cuneiforms, medial three metatarsals and toes (and of the fourth toe), with the intrinsic muscles and the tendons of the leg muscles normally ending therein. In connection with this it is noteworthy that extensor and flexor hallucis longus are entirely absent, flexor digitorum longus has only one tendon and that is joined by extensor digitorum brevis and ultimately inserted into the only toe (the fifth) present, the medial plantar artery is absent and the medial plantar

nerve gives no muscular branches; while the bones, muscles, nerves, and vessels of the outer segment of the foot are practically normal.

2. The large size of peroneus tertius and the abnormal attachment of its tendon to form with that of a separate part of peroneus brevis a tendinous loop under the fibulo-calcaneal articulation.

3. The duplication of certain muscles, *e.g.*, tibialis anterior.

4. The muscle called a peroneus which both arises from and is inserted into the shaft of the fibula and thus could neither have shortened nor subserved any function, yet shows, on microscopic examination, no degeneration, but actual hypertrophy of its fibres.

5. The absence of any representative of the tibia.

6. The absence of abnormal curvature or marked hypertrophy of the fibula.

7. The articulation of the proximal end of the fibula with the lateral condyle of the femur, and of the distal end with the calcaneus.

8. The absence of menisci and cruciate ligaments.

9. The patella is present and the femoral condyles well formed.

10. The malformation and inversion of the calcaneus.

4. *Edmund Cautley's case.*—R.C.S. Museum Teratological Series No. 410.2.

The specimen was removed from the body after death by amputation through the distal end of the femur.

External features.—The leg is greatly shortened both actually and relatively to the foot, which is slightly longer than the leg. The leg is turned inwards (adducted) upon the thigh so that its long axis lies at right angles to that of the thigh. The foot is completely inverted so that its transverse axis is parallel to the long axis of the leg, while its long axis is at right angles to that of the leg. There are seven toes, of which the two most medial have the characters of a third and second in that order from the medial border. Of the lateral five the most medial is like a great toe in form, though relatively short in comparison with the other toes; and there is syndactyly of the true second and third toes.

The skin and subcutaneous tissues had been removed before the present dissection was undertaken. No account of them therefore can be given.

Muscles.—(Fig. 16). The tendons of three only of the muscles of the thigh are present, namely, that of adductor magnus (very small) attached at the normal site on the femur, and those, presumably, of semimembranosus and semitendinosus, blending with the postero-medial part of the capsule (here fibro-cartilaginous) of the knee joint, and through it reaching insertions on the upper end of the tibia. Biceps femoris, gracilis, and sartorius are absent. The structures in front of the lower end of the femur have been removed in amputating the limb, so that the presence or absence of quadriceps femoris and of the patella cannot be stated; but it is certain that there is no ligamentum patellæ.

Popliteus, plantaris, tibialis posterior, and flexor hallucis longus are absent. Triceps suræ is represented by a single flat muscular belly arising from the head and upper end of the shaft of the fibula, the posterior part of the capsule of the knee joint, and, through the capsule, from the lateral condyle of the femur. The tendo calcaneus has a normal attachment. Flexor digitorum longus is double, consisting of a larger and a smaller belly arising together from the shaft of the fibula. The two tendons remain separate in the leg, but blend in the sole of the foot to give off five tendons to the lateral four toes and to the lateral of the two toes medial to the great toe. From these tendons six lumbricals arise and pass to the lateral side of the medial two and medial side of the lateral four toes. Flexor digitorum brevis divides into two parts, from the medial of which two tendons pass to the two most medial toes, while from the lateral two tendons pass to the true second and fourth toes. Abductor digiti quinti is normal; but abductor hallucis is absent, as is also quadratus plantæ. Both oblique and transverse heads of adductor

hallucis are present. They join before being inserted into the base of the toe on the medial side of the hallux; and at their junction is attached a muscle—presumably the lateral head of flexor hallucis brevis—which arises from the metatarsal of the most medial toe. Six dorsal and four plantar interossei are present. The muscles of the lateral four interosseus spaces are normal. The additional three lie in the medial two inter-spaces, and consist of two dorsal interossei inserted on either side of the toe next to the hallux, and a plantar inserted on the lateral side of the most medial toe.

Tibialis anterior and extensor hallucis longus are absent. Two extensores digitorum longi are present. The medial and smaller muscle arises from the head of the fibula and front of the capsule of the knee and gives tendons to the medial two toes. The lateral has a normal origin from the fibula and supplies tendons for

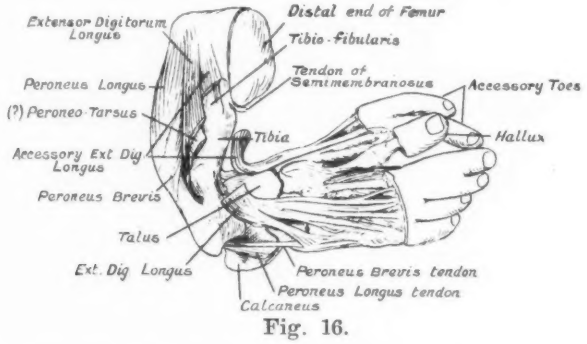

Fig. 16.

the lateral three toes and also to the base of the most lateral (*i.e.*, the true fifth) metatarsal, though the line of separation of a peroneus tertius is not evident in the muscle itself. Extensor digitorum brevis is composed of three bands, of which two arise from the medial border and one from the lateral side of the dorsum of the tarsus. The lateral part gives off three tendons to the true second, third, and fifth toes, and then converges with the medial portions into an expanded tendon overlying the cuneiforms and inserted into the base of the metatarsal of the hallux.

Peroneus longus and brevis have a normal origin. The manner of insertion of their tendons is also normal, except that the tendon of peroneus longus gives off a slip attached to the calcaneus and extends across the sole to the bases of the most medial two metatarsals.

Three abnormal muscles are also present: (i) A large tibio-fibularus running downwards and medially from the upper half of the shaft of the fibula to the upper third of the tibia. (The proximal border of this muscle is attached to and separated from the cavity of the knee joint by a fibro-cartilaginous plate described below.) (ii) A small muscle arising from the front of the tibia close to the distal articular surface and passing distally to be inserted into the base of the most medial metatarsal. (iii) A slender muscle taking origin from the upper half of the shaft of the fibula deep to extensor digitorum longus, and inserted into the lateral side of the talus. This may be a peroneo-tarsus.

Bones.—The distal end of the femur consists of two imperfectly-formed condyles separated by a faintly-marked intercondyloid groove and fossa.

The tibia is represented by a short straight bone, stouter than but only one-third of the length of the fibula. Removal of a strip from its whole length shows that it is entirely cartilaginous. The normal subdivision of the bone into shaft and epiphyses is not evident, and it is probable that the epiphyses are entirely absent. The upper end is covered with articular cartilage on its proximal aspect, and articulates, a part of the cartilaginous plate intervening, with the side of the medial condyle of the femur. The distal end articulates directly with the talus.

The fibula is outwardly curved in its long axis, but is not abnormally thick. The head is ill-defined and articulates with the lateral condyle of the femur, the cartilaginous plate intervening as in the case of the tibia. The distal end articulates with the lateral side of the talus.

Talus, calcaneus, and navicular are fused to form an irregularly-shaped bone. There are four cuneiforms all borne by the navicular part of this fused bone. The medial two cuneiforms support the medial two metatarsals (of which there are seven); the third cuneiform supports the metatarsal of the hallux and true second toe, and the fourth that of the true third toe. The cuboid articulates with the lateral two metatarsals.

The toes have been sufficiently described above. They all have the normal number of phalanges.

Articulations.—The articular surfaces entering into the knee joint are, as mentioned above, those on the distal end of the femur, the proximal end of the tibia and the head of the fibula. But the most interesting and important constituent of the joint is a plate of fibro-cartilage which covers the articular surfaces of both tibia and fibula, fills in the gap between these two surfaces, and blends with the capsule of the front and back of the joint. This cartilage is partly divided into two parts by a pad of fat and it receives part of the insertion of semitendinosus and semimembranosus. Probably it represents the menisci partly united. The transverse axis of the joint is abnormal, being parallel with instead of at right angles to the long axis of the leg. In other words, the femur articulates with the side instead of with the proximal end of the leg.

The tibia and fibula form separate articulations with the talus. No communication exists between the joints; but a strong ligament binds together the distal ends of the tibia and fibula.

In the articulations between the talo-calcaneo-navicular and the cuneiforms and the cuboid there is one joint cavity. Well-formed joints exist between the latter bones and the metatarsals, between those and the toes, and in the toes.

Summary.

1. The shortening of the leg.
2. The presence of an additional cuneiform and second and third metatarsals and toes, carrying additional interossei and lumbricals, on the medial side of the foot and to the medial side of the first metatarsal and hallux.
3. The absence of the tendons of some of the thigh muscles and of some of the muscles of the leg and foot.
4. The duplication of flexor and extensor digitorum longus and bifurcation of flexor digitorum brevis, corresponding to the additional medial segment of the foot.
5. The presence of a tibio-fibularus and of a probable peroneo-tarsus.
6. The imperfectly-formed femoral condyles and intercondyloid fossa.
7. The short cartilaginous tibia undifferentiated into its normal subdivisions and probably the shaft only, the epiphyses being absent.
8. The outward curvature and lack of hypertrophy of the fibula.
9. The formation of the knee joint between the distal end of the femur and the cartilaginous plate covering the medial side of the upper end of the fibula and the upper end of the tibia, the axis of the joint being in line with, instead of at right angles to, the long axis of the leg, and the cartilaginous plate probably representing the partly united menisci.
10. The separate articulation of tibia and fibula with the talus.
11. The fusion of talus, calcaneus, and navicular.

5. *Thomas Bryant's case* (1883)—R.C.S. Museum Teratological Series No. 439.

The specimen is the right leg of an infant. The leg has been removed by disarticulation at the knee. No description of the femur or knee joint is possible therefore. A superficial dissection had been carried out before the present dissection was undertaken; so that the condition of the skin and subcutaneous tissues cannot

be stated. Moreover it is not possible to state the difference (if any) of the size of the limb from the normal, as the age of the child from whom the specimen is derived is unknown.

The leg is straight, the fibula showing none of the curvature present in most specimens. The foot is inverted through 90°, its long axis remaining at right angles to the leg. There are five toes, of which the third and fourth show the condition of syndactyly; the first is short and only recognisable as the hallux because it possesses two segments.

Muscles.—(*see* Figs. 17, 18 & 19). The musculature of the limb is highly abnormal, in the absence of some muscles, in the irregularity of others, and in the presence of muscles which are not found in the normal limb. It is very difficult therefore to determine the place and value of the muscles seen on dissection. There are several very interesting and instructive features.

With the exception of gastrocnemius there is no trace of the thigh muscles which are inserted in the leg. In the leg all the muscles present are well developed, and were apparently healthy.

Peroneus longus and brevis are normal in size, origin, and insertion, except for the manner of insertion of the tendon of the former: this expands triangularly under the cuboid; the expansion is joined on the proximal side by the tendon of flexor

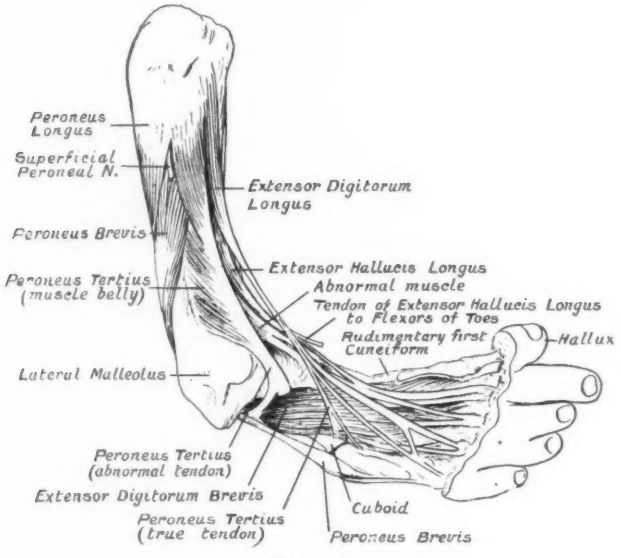

Fig. 17.

hallucis longus (*vide infra*) while the lateral border merges into the fascia covering the muscles of the fourth interosseus space and the fifth metatarsal. The peroneus longus tendon runs through the expansion and then divides, one part ending in the medial cuneiform and base of the second metatarsal, the other running into the first dorsal interosseus muscle.

Extensor digitorum longus has a small fleshy belly arising from the antero-lateral aspect of the upper end of the shaft and the head of the fibula, from which two tendons arise: the medial gives off a slip to the fourth toe, and another which, after partly fusing with the inner margin of extensor digitorum brevis, runs on to the third toe; the lateral supplies a tendon to the fourth toe, and another, which ends in the fascia covering the fourth interosseus space and undoubtedly represents a peroneus tertius tendon. The muscle arising in the position normal to peroneus tertius, however, has no connection with this tendon. It is a large muscle with a much extended origin, so that it arises from the whole length of the shaft of the

fibula, immediately in front of the other peronei; but though the upper portion of its origin is in common with that of extensor digitorum longus, it soon separates from that muscle, and a strong tendon develops along its anterior border and runs to be inserted by two limbs into the under surface of the talus and the lateral surface of the calcaneus. This muscle is also undoubtedly peroneus tertius; apparently the muscle and its normal tendon have developed separately, or have become separated during development.

Extensor digitorum brevis is normal except that its most medial tendon runs to be inserted like a long extensor tendon into the terminal phalanx of the second toe, instead of into the base of the first phalanx of the first toe. This tendon is joined in its course by a small tendon from a muscle presumed from its site of origin to be extensor hallucis longus. Its origin is from the upper three-fifths of the shaft of the fibula immediately medial and deep to extensor digitorum longus and peroneus tertius, and it crosses anterior to the deep peroneal nerve and anterior tibial artery. The above-mentioned slip constitutes only a tiny portion of its tendon, the major portion of which runs round the medial border of the tarsus into the sole, where it takes part in the formation of a tendon from which the flexor digitorum longus tendons arise. This then is a muscle whose tendon has become diverted to make the muscle subserve a function very different from that of the normal. In direct continuation to extensor hallucis longus in its line of origin is another muscle, arising from the distal two-fifths of the shaft, whose tendon ends in a dorsal expansion over the distal part of the tarsus. Whether or not this is to be regarded as an additional part of extensor hallucis longus cannot be stated. Neither can it be said whether a tibialis anterior is present or not: there is no muscle having an insertion similar to that muscle, though there is a small muscle arising from the head of the fibula immediately in front of and on the same level as extensor digitorum longus which may be regarded as a tibialis anterior. This gives off a slender tendon which ends in a fibrous mass to be described below, though its fibres are traceable onwards into a tendon which fuses with that of extensor hallucis longus to form the flexor digitorum longus tendon mentioned above. A similar small muscle adjoining and partly fused with the above muscle has a tendon also joining the fibrous mass, and is possibly an accessory tibialis anterior.

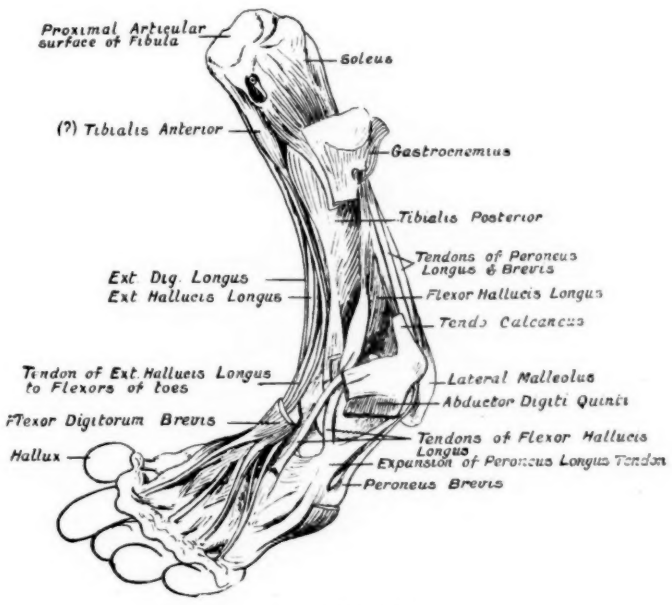

Fig. 18.

On the posterior aspect of the leg the muscles can be named with greater certainty. Of triceps suræ both heads of gastrocnemius are present, and soleus is a large muscle arising from the posterior aspect of the head of the fibula; the tendo calcaneus is inserted normally. Plantaris is absent, as is also popliteus. The large tibialis posterior has a normal origin from the fibula; and a tiny muscular bundle which runs from the head of the fibula to the proximal end of the part arising from the shaft of the bone, and is separated from the intervening bone by the anterior tibial artery, probably represents part of the tibial origin of the muscle. The insertion is into the fibrous mass mentioned above. This is merely a fused mass of tendons attached to the upper surface of the talus and the capsule of the ankle joint. Arising from the shaft of the fibula immediately lateral to tibialis posterior is a large muscle which must be regarded as flexor digitorum longus, though it is inserted entirely into the fibrous mass. Flexor hallucis longus, though it has a normal origin, is also peculiar in that some of its insertion is into this mass. But more peculiar is the remainder of its insertion, which is by two tendons, both of which run into the sole of the foot, the one to end in the expanded peroneus longus tendon, the other into the fascia covering the fourth interossoeus space.

From the fibro-tendinous mass formed by the fusion of the tendons as described, the origin of the tendon entering into the formation of the flexor digitorum longus tendon has been already mentioned. From it also one head of flexor digitorum brevis arises, the other head having the normal origin of the muscle. There are three

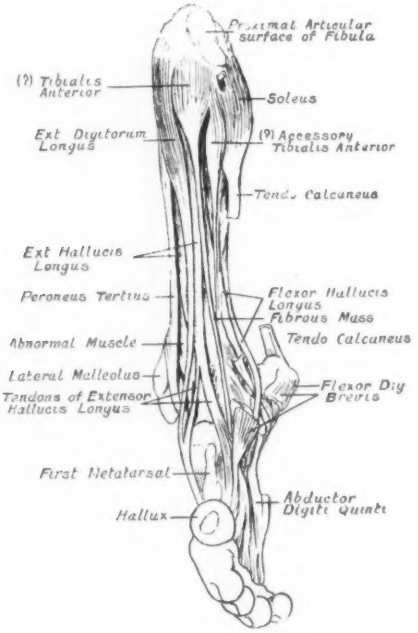

Fig. 19.

tendons only to this muscle, running to the second, fourth, and fifth toes. The flexor digitorum longus tendon gives off four tendons to the lateral four toes. The lumbricals are normal in position and attachments. From the deep surface of the long flexor tendon an abnormal muscle arises; it is inserted into the heads of the third and fourth metatarsals, and its significance is obscure. Abductor digiti quinti, flexor digiti quinti brevis and the interossei are normal; but quadratus plantæ, adductor and abductor hallucis, flexor hallucis brevis and the flexor hallucis longus tendon are all absent.

Vessels and Nerves.—The main vessels and nerves are present and the arrangement of the main trunks (having regard to the altered position of muscles) is practically normal.

Bones and Joints.—The tibia is entirely absent without fibrous or cartilaginous representative. The fibula is straight and not abnormally thick. The proximal end bears a slightly concave articular surface on the postero-medial aspect of the head, which doubtless articulated with the femur. The articular surface on the distal end is in the normal position and is applied to the facet on the postero-lateral aspect of the talus. The cavity of the joint thus formed is small, but the capsule and ligaments are very thick and strong. The plane of this modified ankle joint is vertical. It is at this joint that the inversion of the foot is effected.

Talus, calcaneus and navicular are fused to form a compound bone. Each portion is fairly well formed and clearly recognisable. The sinus tarsi is absent. The compound bone through its navicular part articulates with two cuneiforms only. These are presumably the second and third, as they support the second and third metatarsals. These, and the fourth and fifth borne by the cuboid (normal in form and articulation), are normal; but the first metatarsal is much smaller and shorter than the others. It is composed of two segments—with a joint between—the distal of which is bony and is probably the true metatarsal, while the proximal is cartilaginous and attached by fibrous tissue to the second cuneiform, and probably is a very poorly developed first cuneiform.

There are five toes, which have been sufficiently described above.

Summary.

1. The irregularity of attachment of some of the muscles, viz.:—

   (*a*) The dissociation between the muscle belly and the normal tendon, illustrated by peroneus tertius.

   (*b*) The diversion of the normal insertion so that the muscle is made to subserve an entirely different and even opposite function, *e.g.*, extensor hallucis longus supplying the major part of the long flexor tendon of the toes.

   (*c*) The abnormal insertion of a tendon running an otherwise normal course, *e.g.*, that of flexor hallucis longus into the tendon of peroneus longus and the fascia of the fourth interossoeus space.

   (*d*) The termination of some of the leg muscles in a fibrous mass with the origin of short flexor tendons therefrom (a condition analogous to that which is found in the apes), *e.g.*, tibialis posterior and flexor digitorum longus joining the fibrous mass, and flexor digitorum brevis deriving partial origin therefrom.

2. The presence of abnormal muscles: for example, the muscle described as possibly a separate part of extensor hallucis longus; and that which springs from the deep surface of the long flexor tendon of the toes and is inserted into the head of the third and fourth metatarsals.

3. The absence of normal muscles: for instance, popliteus, quadratus plantæ and the intrinsic muscles of the hallux.

4. The complete absence of the tibia.

5. The absence of hypertrophy and curvature of the fibula.

6. The fusion of the calcaneus, talus and navicular.

7. The partial failure of growth of the first cuneiform and first metatarsal.

The most striking thing about the specimen is that the abnormal features are mainly confined to the inner border of both the leg and foot. Moreover, not only are bones absent or poorly developed in this area, but here also muscles have gone astray in their attachments, have failed to form, or appear in abnormal situations. It is evident thus that the disturbance of the mesoderm which must have underlain these abnormal features was mainly confined to the inner side of the limb, and was not confined solely to the bones, but extended to all the skeletal structures of the part.

6. *H. H. Clutton's case* (1896)—R.C.S. Museum Teratological Series No. 441 A. & B.

The specimens were prepared and described by H. S. Targett in 1896. The following is Targett's description slightly altered:—

1. *Left leg and foot macerated.*—There is but one bone in the leg which has the character of a fibula. It measures 7½ inches in length; the upper end is cartilaginous, but without the normal facet, and it appears to have been connected with the femur by fibrous adhesions. The shaft of the bone is somewhat curved, convexity outwards; but is not specially deformed though hypertrophied. The lower end of the diaphysis, together with the epiphysis (lateral malleolus) are united with a compound talo-calcaneo-navicular to form the ankle joint, in such a manner that the sole of the foot looks directly inwards, and the articular surfaces of this modified ankle joint are in a vertical plane instead of being horizontal.

The foot, as a whole, is in a position of marked varus, the dorsal surfaces of the fourth and fifth metatarsals being directed towards the ground. The forepart of the foot is also much adducted, so that its inner border is rendered very concave with the concavity upwards. The chief bone in the tarsus is very irregular and probably represents a fused talus, calcaneus, and navicular. The line of fusion between talus and calcaneus is quite distinct on the inferior (outer) aspect of the foot; but the sinus tarsi is absent. In front the calcaneal portion of the compound bone articulates with a normal cuboid which bears the two outer metatarsals. The talo-navicular portion of the bone articulates in front with two bones which probably represent the first and third cuneiforms, which in turn support the three medial metatarsals. Thus the second cuneiform is absent. The three middle metatarsals show the longitudinal torsion of their diaphyses which is common in severe varus.

2. *Right leg and foot dissected.*—Peroneus tertius is very large, and tibialis anterior with extensor digitorum longus are held in place by a strong ligamentum cruciatum cruris around which they play in consequence of displacement of the foot. Peroneus longus and brevis are also very large; but soleus and gastrocnemius are small and take origin from the fibula. In the sole of the foot the muscles do not appear to vary much from the normal, though small and displaced by the position of the limb.

The upper end of the right fibula shows fibrous adhesions by which its cartilage was connected with the corresponding femur.

7. *J. Bland Sutton's case* (1892).—R.C.S. Museum Teratological Series No. 441.

The specimen consists of the macerated bones of the left leg and foot. The tibia is totally absent. The fibula is abnormally short for the age of the individual from whom the specimen is derived. It is, however, of normal thickness and is not curved. The proximal extremity is covered with articular cartilage and has a flattened surface anterolaterally, which may have been in apposition with the femur. On the medial aspect of the distal end is a slightly convex articular surface for the talus and calcaneus. All the bones of the tarsus are present; but all are malformed, especially the talus. The calcaneus and talus are partly fused, though the sinus tarsi is present The metatarsals are all present and well formed. The digits are normal except that the second and third phalanges of the fifth are fused. The articular surfaces of the ankle joint are that described on the distal end of the fibula, and contiguous surfaces on the proximal end of the talus and upper surface of the calcaneus. (A short description of the soft parts was given by the donor(5) when originally publishing the case.)

Summary of Anatomical Appearances and Abnormalities.

From a consideration of the above cases personally dissected and described with the remaining specimens of the Royal College of Surgeons Museum, together with a study of the anatomical descriptions given by other

writers, a general survey of the structure of, and abnormalities which may be found in, a limb with congenital absence of the tibia, can be given. (It may be remarked how few detailed dissections of specimens of congenital tibial defect have been undertaken. Of the English cases hitherto published, full anatomical descriptions have been given only by Symington and Craig, and by J. S. McLaren. In the reviews of the subject by Launois and Küss, and by Nuzzi, fairly full accounts of the pathological anatomy are given; but the accounts are deficient with regard to the musculature, merely stating that the abnormalities of muscle are extremely variable, inconstant, and of no practical importance—a statement which our own study proves to be fallacious.)

The most striking features are:—

1. The alteration in structure is not confined to the partial or complete absence of the tibia. In all the specimens personally examined, and in all of those described by other workers where a minute dissection has been performed, all the parts, mesodermal and often even epidermal in origin, have been affected.

2. Moreover, the disturbance is not confined to the leg, or even to the leg and foot, but affects the whole lower limb.

3. The abnormal appearances are found in the leg and foot in the main, though not entirely, on the medial (tibial) side, where, moreover, they may either be limited to one part or affect the whole.

4. The changes are not solely suppressive or atrophic. It may, in fact, be doubted if any of them are to be looked upon as "atrophic" in the literal sense of the word. Suppression undoubtedly occurs, as illustrated by the absence of bone or muscle; but disturbance of development of an opposite kind also is found, often conjointly, in the presence of abnormal and double muscles, and of extra segments of the tarsus, metatarsus or toes. Noteworthy also is the constantly healthy condition of the parts, particularly the muscles, some of which may even be much larger than normal, and none of which show degeneration of any kind.

5. The curious and, in interpretation, often puzzling arrangement of the musculature in many specimens, particularly in regard to the dissociation between the muscle belly and the normal tendon, and to the extraordinary transposition of tendons into insertions which make muscles subserve functions which are the reverse of the normal.

6. The tendency to reversion to the structure of lower species, seen in the fibulo-femoral articulation, and in the musculature, *e.g.*, by the presence of such muscles as tibio-fibularus.

7. The presence and persistence without wasting or degeneration of a muscle, seen in one or two specimens, unable to contract and apparently functionless: a physiological curiosity.

8. The tibia may be entirely or partly absent, or may be represented either by fibrous tissue, tendon, or cartilage.

9. The frequent association of dimples, grooves, constrictions and umbilications of the skin of the leg.

The investigation of the anatomy of the thigh has been confined in our own and all other recorded cases (except in one of Ollerenshaw's[23] cases, where, however, no detailed account is given) to an examination of the structure of the distal end as seen at operation and of the tendons of thigh muscles which are inserted in the leg. With regard to the hip, however, Launois and Küss[18] state that luxation is very frequent, and Nuzzi[22] mentions it as an associated abnormality sometimes present. It was not present in any of the cases we have examined; but in Laming Evans's second case a skiagram showed absence of the ossific nuclei of the head of the femur and of the pubic bone on the same side. In most cases the distal end of the femur is imperfectly formed: the condyles and the intercondyloid fossa may be rudimentary or absent. In cases of partial defect of the tibia where the upper end has been present, the femur is usually normal. The thigh muscles which pass to the leg are frequently abnormal, absence of one or more being a constant feature in our specimens and alterations of insertion being seen frequently. The length and circumference of the thigh are commonly slightly smaller than those of the opposite side.

The patella, contrary to the statements made on clinical observation alone in the earlier recorded cases, is present in most cases, though it may be small and its ossification delayed. This is what one would expect, since the patella is not to be regarded as a homologue of the olecranon depending on the existence of the tibia, but as a true sesamoid of the quadriceps tendon, and thereby a part of the first and not of the second segment of the limb. That it is frequently small and sometimes absent is probably due to the fact that the quadriceps itself may be ill-developed or deficient.

A well-formed joint between the thigh and leg is usually present. Where the upper end of the tibia is present the knee joint differs little if at all from the normal. When the tibia is completely absent the joint is formed between the proximal end of the fibula and the distal end of the femur, on its postero-lateral aspect in most cases. Where no joint exists the fibula is bound to the femur by fibrous tissue on its posterior or lateral aspect, and may be displaced upwards some distance into the thigh. A point of practical importance is that the articular surface on the fibula frequently transgresses the epiphyseal line, which may therefore be interfered with by attempted arthrodesis. The menisci and cruciate ligaments are absent in cases of total defect of the tibia.

The tibia may be totally or partially absent, or represented in whole or in part by fibrous, tendinous or cartilaginous elements. In the specimens which have been examined by ourselves and others every grade of tibial defect and representation has been observed: (a) total absence; (b) absence of the lower third or two-thirds (the usual condition in cases of partial defect), or

of middle third; (c) proximal epiphysis or upper end only (often conical with pointed projecting lower end attached to an umbilicated patch of skin); (d) absence of part of the shaft with a fibrous band uniting the upper and lower fragments; (e) fibrous or tendinous strands with and without attachment to fibro-cartilaginous masses at the either end of the leg. In one specimen the cartilaginous shaft without sign of ossification appears to be alone present, the epiphyses being absent.

The fibula is always shorter than normal and usually stouter and incurved. The latter two features are not invariably present: they are absent in three of the specimens we describe. The interosseous membrane may be present where the tibia is merely represented by tendon, or absent and its place taken by muscle where the tibia is actually present. In cases of total absence the membrane is not found.

The ankle joint is formed when the tibia is totally absent between the fibula and the talus, or when the latter bone is absent, the fibula and calcaneus. A representative of the tibia may take part in the formation of the joint. Usually the medial side of the distal end of the fibula articulates with the postero-lateral aspect of the body of the talus, which is thus luxated: it is at this joint, in fact, that most of the varus deformity of the foot takes place.

The bones of the foot share in the abnormality. Almost always there is malformation and fusion of the calcaneus and talus and sometimes also of the navicular. Absence of one or more of the bones of the inner segment of the foot—talus, navicular, cuneiforms, inner three metatarsals and toes, especially the hallux and its metatarsal—is common; but almost equally so is the presence of extra elements—a pre-hallux, cuneiform and particularly a supernumary great toe. Moreover the two conditions may occur in the same limb, a state of affairs which clearly indicates that the cause is not merely an arrest of growth.

The musculature also always shows marked abnormality of structure and arrangement. There may be absence of normal muscles, duplication of normal muscles, presence of additional abnormal muscles, or irregularities of insertion, ranging from mere diversion of tendons running an otherwise normal course, to actual dissociation between muscle belly and the normally inserted tendon. Finally, attention may be drawn again to the occurrence of muscles attached entirely to one bone and persisting, apparently healthy though functionless.

The blood vessels and nerves have been poorly described in all published accounts. In our own specimens the parts were too small to allow of a complete dissection of the nerves and vessels; and in fact such a dissection was considered unnecessary. In these specimens the vessels and nerves appeared perfectly healthy and the main trunks were present and little if at all abnormal in their arrangement. Where they are mentioned in the writings of others they are usually stated to be " practically normal."

Bertaux, who used the method of electrical stimulation to study the anatomy of his specimens, noted the absence of the reaction of degeneration, and found in four legs no abnormality except in one case where the deep peroneal nerve was absent with the muscles it normally supplies.

Cutaneous grooves, constrictions, dimples, umbilications and " scars " occur in the affected limb frequently, particularly over the head and shaft of the fibula, and over the free end of the tibia in the case of partial defect. These skin markings are not true scars: as was proved by histological examination, which showed the absence of scar tissue and mere diminution of the deeper layers of the epidermis at the site of the depression.

VI.—Ætiology.

The current theories of the cause of congenital bone defects are:—(1) The germinal; (2) the mechanical (including the postural and the amniotic); (3) the traumatic.

The germinal theory regards as primary a defect of the mesoblast from which the skeleton of the affected limb is developed. To what this defect is due has not been ascertained; but vascular, microbic, toxic, and endocrinal influences are, without proof, invoked.

The mechanical theories state that interference with normal development and growth is brought about by external pressure on the fœtus, either, according to the postural theory, by malposition *in utero*; or, according to the amniotic theory of Dareste[9] by the abnormal tension of the amnion, itself arrested in development, or by amniotic bands or adhesions formed between the amnion and fœtus as the result of inflammation of the amnion, or by constrictions effected by the umbilical cord.

The traumatic theory regards the cause as violence sustained by the mother during pregnancy and transmitted to the fœtus as it lies *in utero*.

Our study has led us to believe that the theory of primary mesoblastic defect is correct, and that mechanical and traumatic influences are not concerned in the production of congenital bone defects. This view, we believe, is the one now held most widely, and we claim that its truth is now established.

Our investigation of the anatomy has made it clear that the disturbance of development is not confined merely to the tibia, but extends to all the mesoblastic structures of the limb. It has shown also that the disorder is not only of the leg, but of the whole of the limb and even of the pelvis. And, further, it has demonstrated that the changes are not solely suppressive, supernumerary segments, bones and muscles, being almost as often present as normal parts are absent.

The clinical study has revealed that other abnormalities so widely different from the particular one we are considering as cleft palate and cryptorchidism are very frequently associated; and that there is a definite, though not invariable, tendency for the defect to be hereditary and familial

in occurrence. In the latter case, moreover, the defect may be identical in two or more members of the family. Another point has also come out: that when the defect is bilateral there is frequently remarkable symmetry of the affected limbs.

It is manifest from these facts that the cause of congenital bone defects is intrinsic and not extrinsic in action. It is inconceivable that external pressure or violence could bring about the anatomical abnormalities. The suggestion that either of these influences do so becomes highly improbable when we call to mind that they would have to act as early as the sixth week, when the fœtus is only three or four centimetres in length, for by this time the muscles and bones are clearly differentiated.

The traumatic theory is mainly based on the assumption that the " scarring " of the skin and marked angulation of the fibula sometimes seen are due to intra-uterine laceration and fracture, followed by resorption of the tibia. The above clinical and anatomical facts, the frequent absence of any history of trauma, lack of angulation or " scarring," and the histological proof that the skin markings are not true scars, render this theory untenable.

There is little evidence also tf support the mechanical theories. They seem to rest principally on the frequent presence of cutaneous markings on the outer side of the leg and foot and of outward curvature of the fibula, and on the usual limitation of the defects to the lower limbs with associated normal development of the rest of the body. The theories are thus based on very slender evidence; and the facts cited above are enough to disprove them. It is probable that the amniotic anomalies are associated abnormalities due to the same cause as the fœtal mesoblastic defects. Although the cutaneous constrictions may be caused by an amniotic band or the umbilical cord, the dimples, cutaneous scars and grooves are more probably not due to these agents, but are caused directly by the disturbance of limb growth. The facts that they are not true cicatrices, are not present in very many cases, and, when present, are not always at sites where pressure would have occurred, favour the latter view. If these theories were true one would expect to find in records of cases a note that birth was difficult or otherwise abnormal. Such a note is absent in most cases, while in not a few the reverse is stated.

The evidence is, in our opinion, overwhelmingly in favour of the theory of a primary defect of growth of the mesoblast. This opinion is strongly supported by the recently published investigations of Hovelacque and Noel[14]. They observed the development of the lower limbs in a breed of mice commenced by Rabaud in 1909, in which members afflicted with congenital absence of the tibia made their appearance first in 1913, and occurred continuously from then till 1920. They studied both normal and abnormal embryos of every age and size; and their conclusions are summarised here:—

1. The first manifestations of the anomaly are revealed when the undifferentiated blastema first commences to undergo modification.

2. There is no modification in the outline of the fibula; at most there is a slight delay in the appearance of the successive stages.

3. The anomaly is manifested solely in the zone of blastema where the tibia would normally develop. A fibrous tract is formed here, and between it and the fibula the interosseus membrane appears.

4. In certain embryos cartilaginous nodules develop in this zone of blastema, mainly at the upper part near the femur. The continuity of the nodules and the fibrous tract, and the fact that they are parts of the same structure, have been definitely established.

5. Throughout the complete evolution, vascularisation is normally developed in the whole extent of the structure. Thus the idea of a vascular origin of the anomaly may be cast aside.

These observations are very convincing, and with the anatomical and clinical facts we have been able to bring forward, establish, we think, the truth of the germinal theory. With regard to this we feel that it is important to emphasise that the mesoblastic defect is not merely one of temporary or permanent cessation of growth. It is obviously a more profound disturbance than this, since it involves arrest of growth in some elements of the limb with associated abnormal or excessive development of other elements. The underlying cause of the defect is quite unknown. There are no reasons for assuming that it is endocrinal, microbic or toxic action. The subjects of congenital bone defects rarely show evidence of syphilitic or other fœtal disease, and are often born of perfectly healthy parents. Nor are there any strong reasons to support an atavistic theory. Occasional features in dissected specimens suggest reversion to those of lower animal orders; but these are not sufficient evidence on which to base an atavistic theory. Certainly there is nothing to support Gegenbauer's suggestion of suppression of a tibial "fin-ray." Apart from the fact that at no moment in the development of the limbs of the human embryo is there a state comparable to that of the fin of fishes, it is impossible by this theory to reconcile absence of the tibia with the presence of a normal foot and still more of polydactyly. Thus, while it is clear that the cause of congenital bone defects is primarily in the mesoblast itself, the underlying reason for this remains obscure.

VII.—Treatment.

Congenital absence of the tibia has always formed a difficult problem for surgeons, many of whom have taxed their ingenuity in endeavouring to devise means of converting the useless limb into one useful by itself or when aided by an appliance. The great majority of conservative measures attempted have failed; and the reason for this has been the deficient knowledge of the structure and manner of growth of limbs affected with the anomaly. Our study has made the indications for treatment clearer.

In considering these it is necessary to bear in mind that the anomaly is a gross one involving the whole lower limb and not merely the obviously affected segment; that with the tibial bone defect are associated almost invariably defects or other abnormalities of other bones of the limb, and a musculature highly irregular in arrangement and development; and that the deficiency in the limb is not only one of development, but also one of growth. The last is a cardinal point, for, because of it, the leg, abnormally short at birth, becomes progressively shorter relatively to the sound limb as the age of the patient advances towards maturity. This fact has a very important bearing on the question of prosthesis both without and following conservative operative interference, and on that of bone-grafting to replace the congenital defect. Reference will be made to it again.

Until 1875 amputation seems to have been the only surgical procedure undertaken. The credit of being the first to attempt a conservative operation belongs to Albert[1], who in 1877 performed arthrodesis of the knee in a case of total tibial defect by grafting the fibula into the intercondyloid fossa of the femur. He has been followed since then by a number of other surgeons who have either adopted his method or effected the arthrodesis by removal of the cartilage of the fibular and femoral articular surfaces. Combined with one or other of these procedures arthrodesis of the ankle joint by similar methods, and correction of deformities of the knee and foot, were sometimes performed. Attempts have been also made, in cases of partial absence of the tibia, on the same principle of making the fibula take the place of the tibia, to effect union between the free end of the tibia and the fibula—either to the side of the bone or to the distal fragment after osteotomy (Nové-Josserand[21]), or to the head of the bone freed and drawn down (P. Bade[2]). The result is said to have been satisfactory in several cases where one of these measures was done, and in one or two excellent, the patient walking without the aid of an instrument. In a few cases, notably that of Fraser and Robarts[12], another principle, the replacement of the defect by bone-grafting, has been followed. In the case quoted both proximal and distal ends of the tibia were present and the fibula of the normal limb was transplanted into the gap with, it is claimed, a satisfactory result. Of recent years the tendency has been again towards amputation except in selected cases of small partial defects.

It is important to distinguish between cases of total and cases of partial defect, and to consider the question of operative or non-operative treatment of each.

In cases of total defect our opinion is that operative intervention is indicated in all cases whether the abnormality is unilateral or bilateral. We do not agree with the statement of Nuzzi[22] that orthopædic apparatus assures good and correct functioning of the affected limb. An appliance is unavoidably cumbersome and must be progressively raised to compensate for the shortening and we do not advise it. The operation should be that

of amputation at the knee. We are opposed to arthrodesis of the knee and ankle. In the young subject they involve a great danger of damage to the epiphyseal cartilages, and thereby of interference with the already deficient growth; they do not abolish the necessity for an orthopædic appliance; and the anatomical peculiarities prevent the formation of a useful limb by this procedure even when combined with the correction of deformities. A bone graft, or transplantation, of the opposite fibula, is also obviously inadvisable in total tibial defects: even if the graft survives it cannot prevent the

Fig. 20.

Amputation at the knee. Plaster peg-leg fitted.

progressive shortening of the limb upon which depends a great part of the deficiency of function. Except in adult subjects with well-formed femoral condyles we favour disarticulation at the knee rather than supracondylar amputation. By disarticulation interference with the growth of the femur is avoided. The disadvantages of this procedure in a normal limb, namely, the difficulty of fitting a prosthesis over the broad distal end of the femur and of making the artificial knee joint at the same level as the knee joint of the sound limb, do not apply in most cases of congenital absence of the tibia. In them the thigh is usually half an inch or more shorter than that of the

healthy side, and the femoral condyles absent or poorly developed. Even if platymeria or forked platymeria of the condyles were present we would prefer to excise or round off the condyles rather than to amputate above them. It is of little importance whether or not the patella is left in the flap; on the whole it is better to remove it. The operation should be undertaken early, preferably during the second year when the child is attempting to walk. If it is done then and an extensible peg-leg applied, and later, if desired, an artificial limb, the normal education of the child can proceed uninterruptedly, and the femur and thigh muscles will not suffer from disuse atrophy. The operation of disarticulation at the knee in infancy is attended with no or very little shock, and the only objection to it at this age is the possibility of the later formation of a conical stump. There is, however, no need to fear this. (*See* Fig. 20.)

In partial defects we also advise amputation, except when there is present a considerable portion of the proximal part of the tibia with a well-formed knee and a foot which is plantigrade or can be made so. The same objections to an orthopædic appliance and to conservative operations hold good, though to a less degree, for partial as for total defects. Unless the defect is such as stated in the above reservation conservative measures hold out little hope of achieving a good functional result. The modern artificial limb is far more useful, less noticeable, and less cumbersome than any orthopædic appliance which can be fitted to one of these cases, whether a conservative operation has or has not been performed. A prosthesis is almost always needed after such an operation, because the operation cannot correct the shortening of the leg, and it cannot make the leg strong enough to bear the weight of the body steadily on a raised boot. The prosthesis is difficult to apply, inevitably heavy and clumsy, and cannot compare in efficiency with an artificial limb.

In the type of case mentioned above as a reservation it may be worth while to attempt a reconstructive operation. The principle of this will be either to make the fibula do the work of the tibia by uniting the distal end of the defective tibia to the fibula, or to obliterate the defect of the tibia by transplanting the fibula from the sound limb into it, or by a grafting of an autogenous piece of bone. Operations to stabilise the ankle and to correct deformity of the foot and knee should be undertaken later if necessary.

The best results from conservative procedures are to be expected where there is present a large portion of the tibia, especially if both the proximal and distal ends exist, and the proximal end with the knee joint is well-formed. Success cannot be expected if the defect is of the proximal end.

VIII.—Conclusions.

1. Congenital absence of the tibia is one of the rarest of congenital malformations and the rarest malformation of the lower limb. The number of recorded cases is now 105.

2. Tibial absence is rather more commonly total than partial, unilateral than bilateral, and right-sided than left sided.

3. Other abnormalities are frequently associated; but rarely is there any evidence of fœtal disease.

4. The characteristic signs are: (*a*) Shortening of the leg; (*b*) flexion and adduction of the knee; (*c*) inversion of the foot. Radiographic examination is very valuable to establish the diagnosis and to reveal other anomalies of the bones of the limb.

5. The diagnosis is not difficult. Fibular defects and congenital equinovarus need elimination.

6. The anomaly involves the whole lower limb and not merely the tibia. Defects and other abnormalities of other bones of the limb and a musculature highly irregular in development and arrangement, accompany the defect of the tibia.

7. The defect is of both development and subsequent growth, so that there is progressive shortening relative to the sound leg till maturity is reached.

8. The changes are not solely suppressive. Supernumerary bones and muscles and abnormal muscles are almost as often present as others are absent. Moreover, the changes are not atrophic or degenerative.

9. The tibia may be totally or partially absent, or represented in whole or in part by fibrous tissue, tendon, or cartilage. In partial defects it is almost always the distal part of the bone which is absent. Absence of the proximal end and of the middle portion have been each recorded once only.

10. The cause is defective development of the mesoblast under an influence at present unknown, but not traumatic, mechanical, vascular, or atavistic. Amniotic anomalies when present are probably due to the same influence. The mesoblastic changes have been observed in fœtal mice from the earliest stages of tissue differentiation.

11. Disarticulation at the knee followed by the application of a peg-leg or artificial limb is the best line of treatment. Conservative operations are indicated only in cases of partial defect when the gap is small and limited to the middle portion or distal end of the tibia. In all other cases treatment by conservative operations or by orthopædic appliances is inadvisable. Conservative operations should be based on one of the following principles: (1) The utilisation of the fibula to take the place of the tibia; or (2) the insertion of an autogenous graft to fill the gap in the tibia. An appliance is almost always needed subsequently and the results are rarely satisfactory.

We are indebted to Sir Arthur Keith for permission to use the specimens in the Royal College of Surgeons Museum, and for much valuable help and advice. We also wish to thank Dr. Edmund Cautley, Mr. H. A. T. Fairbank, and Mr. R. C. Elmslie for allowing us to describe their cases and specimens; Dr. W. H. Coldwell for photographs and skiagrams and Mr. S. A. Sewell for his drawings.

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SCHOLASTIC AND INTELLIGENCE TESTS.

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Tests of scholastic ability and of general intelligence have been in use for several years, mainly in connection with the certification of mental defect in the legal sense.

Mental defect in this sense is, owing to the terms of definition in the Mental Deficiency Act, 1913, much more common among the child population than the adult, and it is stated (Cyril Burt, " Mental and Scholastic Tests," L.C.C., p. 173) that roughly one-third of the children certified as mentally defective and educated in a Special Day School will on leaving school at the age of 16 have sufficient intelligence to manage their practical affairs and consequently will no longer be certifiable as mentally defective.

This position arises because of the definition of the term feeble-minded persons, which is " persons in whose case there exists from birth or from an early age mental defectiveness not amounting to imbecility yet so pronounced that they require care, supervision and control for their own protection or for the protection of others, or, in the case of children, that they by reason of such defectiveness appear to be permanently incapable of receiving proper benefit from the instruction in ordinary schools."

It is those children who are certified mentally defective in this sense by the certifying medical officers of the Education Authorities who are suitable for instruction in a Special School for mentally defective children.

The category certainly includes many children who would not be designated mentally defective by pure medical clinicians, as a result of ordinary clinical examination, and in the light of conventional medical training and standard (hospital, institution, general practice). Undoubtedly these borderline children benefit scholastically by special educational facilities, but, as the term mental defect carries with it commonly a stigma, it would appear that advantage might be derived from restriction of the term to a more purely medical basis, with some other term applicable to the cases more purely scholastic or educational.

When dealing with possible mental defect in the legal sense, the certifying officer, apart from personal examination, has two main sources of aid in forming an opinion—the school reports and the intelligence quotient.

Of the cases of suspected mental defect which have come before me in such a capacity during the past 15 months, I find that 1,000 have been tested by Prof. Burt's revision of the Binet-Simon tests. I endeavoured in every case to form my own opinion in the light of the legal instructions, and so far as possible to be not unduly swayed either by anomalies in the home or school or by other opinions or tests. The tests were in all cases

carried out under the immediate direction of the Lady Superintendent of the Special Schools. I do not think any clinician of experience is naturally swayed by cut-and-dry tests for general application, and I cannot feel that I in any way exalted the importance of the Binet-Simon results in forming my individual opinion.

Of the 1,000 children, 293 were diagnosed as dull and backward, or dull or backward; 44 were certified physically defective, 143 were certified imbecile or idiot; and 520 were certified feeble-minded, and therefore suitable for education in a Special Day School for mentally defective children.

The relative proportion of the figures in the different categories is here of no significance. Special circumstances were attached to some of the examinations, and from 200 to 300 other children were in addition certified in one or other of the four categories without Binet-Simon tests being made.

As these children were all referred to me as cases of suspected mental defect, I have bracketed the figures for the physical defectives with those for the dull and backward in order to obtain a clear-cut comparison between this combined dull and backward group and the feeble-minded.

The tabulated results of the tests show the following figures:—

I.Q.	25 or under.	25 to 50	50+	60+	70+	80+	90+	100+	Total Cases.	
Dull or backward or both...	—	—	10	52	112	76	25	18	293	
Physically defective ...	—	—	3	12	17	7	3	2	44	
	—	—	13	64	129	83	28	20	—	337
Feeble-minded	—	48	140	208	117	7	—	—	—	520
Imbecile or idiot	10	37	36	6	4	—	—	—	—	140
	—	—	—	—	—	—	—	—	—	1,000

I find from the figures in this particular series that for dull and backward children the common quotient is in the late seventies, while for educable mental defectives it is in the early sixties. The quotient is, at best, *one* aid to a decision regarding the individual, but it is an important one. The decision is influenced by various circumstances apart from it, *e.g.*, character cases, etc., and the quotient itself varies in significance according to age, whether scholastic or intelligence failure, etc., and to some such conditions the unusually higher quotients among those here noted are due.

Intelligence tests are in many instances valuable for the practitioner. This is particularly the case for patients with physical defects who suffer from long-continued or recurrent ailments, and on the mental side for cases of scholastic retardation or character anomalies. Chorea, neuropathies generally, and paralytic cases are frequently examples of a combined physical and mental defect, and here scholastic combined with intelligence tests often give most valuable information as to ætiology, prognosis and desirable procedure.

A STUDY OF GASTRIC ACIDITY IN INFANTS.

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The following study of gastric acidity in infants was undertaken to investigate possible differences of acidity in various clinical entities. A study of normal cases was made for purposes of comparison, not only with our own abnormal cases, but also with the cases recorded in the literature (Table I.). It was obvious that, for the completely normal infant under

TABLE I.

Authority.	Type of Case.	Feed.	Average Maximum Gastric Acidity expressed as pH.
Davidsohn (3)	Infants under 4 months	$\frac{1}{3}$ milk ...	5·1
		$\frac{2}{3}$ milk ...	4·9
		Whole milk ...	4·7–6·2
	Infants up to 7 months	Breast ...	4·48
	Infants over 7 months	,, ...	2·92
Marriott (7)	Normal Infants 1-12 months	Breast ...	3·75
		Sweet cow's milk	5·3 immediately
			4·75 after some time on feed
	Sick Infants 1-12 months	Breast	4·75
		Sweet cow's milk	5·35
Babbott and Others (1)	Hospital cases not seriously ill	Test feed approximately skim milk	3·2-5·0
Kronenberg (5)	Normal Infants...	Breast ...	5·0
		Cow's milk and test feeds ...	4·0
Parsons ... (8)	Marasmic cases ...	Artificial feeds Fresh or dried cow's milk	Free hydrochloric some time during digestion

7 months, our average figures of pH 2·70 for breast fed children and pH 3·5 for the artificially fed, indicate much higher acidities than those recorded by other writers. Davidsohn[3], Marriott[7], and Kronenberg[5] give figures ranging from pH 3·75 to 5·0 for normal infants up to 7 months, which would correspond to lower average acidities. Davidsohn[3], for normal breast fed infants over 7 months old, finds an average acidity of pH 2·92, practically the same value as our figure for the same type under 7 months. Babbott and co-workers[1], working with a skim milk feed and using convalescent cases which were considered normal as far as their gastric function was concerned, found a wide range of acidity, from pH 3·2 to 5·0.

Further observations on underweight, but otherwise normal, infants indicated that, contrary to the usual teaching, given comparable cases, with the possible exception of the completely normal, the average maximum gastric acidity is the same, regardless of the nature of the feed.

These findings are set out in full below, together with a series of observations on sick infants.

Before discussing the methods used and the findings, a brief note on the terms used will perhaps be useful. The true acidity of a solution is the measure of the hydrogen (H) ions present in that solution. For example, a N/10 solution of hydrochloric acid contains 1/10 molecular weight of HCl in grammes dissolved in a litre and this HCl is 91% dissociated at this dilution: the hydrogen ion concentration is therefore $9{\cdot}1 \times 10^{-2}$. To avoid the use of so many figures Sörenson introduced the exponent pH*, as the expression of the hydrogen ion concentration, or true acidity:—for a N/10 HCl solution pH equals 1·04. The disadvantage of the exponent pH is that as the acidity increases it becomes less and *vice versa*, *e.g.*, a neutral solution has a pH of 7·0, figures below this (pH 2·0) indicate acid solutions and figures above (pH 8·0) alkaline ones. The exponent pH will be used throughout the following papers to express the true acidity of the solutions under consideration.

A " buffer " substance is one that allows the addition of an acid or alkali to a solution without an appreciable alteration in the reaction (acidity or alkalinity) of the solution. The protein of milk is such a substance; it, so to speak, " mops up " added acid, so that till sufficient acid has been added to saturate the buffer, there is only a slight increase in the acidity or hydrogen ion concentration of the solution.

The titratable acidity, determined with caustic soda, gives a measure of the total acidity, both free and combined. It is, therefore, an index of the acid excreted by the stomach.

The term " free hydrochloric acid " is used to denote the hydrochloric acid which is not linked to the " buffer substance " of the stomach contents, but is present in the uncombined condition.

*pH equals the logarithm to the base 10 of the concentration of H ions in grammes per litre, the negative sign being understood.

Methods.

No definite test meals were given, but the stomach contents were removed and examined after the ordinary feed. A soft rubber catheter (Jacques) was passed, generally portions of the stomach contents were expelled through the tube; failing this, portions were removed by a syringe. There was generally no difficulty in obtaining samples, but if there was excessive salivation or retching samples were rejected.

Either the whole stomach content was removed or the fractional method of sampling was used. Babbott[1] and Davidsohn[3] have discussed the errors in these methods and, as in two samples taken immediately one after the other the differences in pH may be as great as 0·3, it is essential, if the single sample method is used, to attempt to empty the stomach. In the fractional tests, this error is recognised. From a study of the curves of gastric acidity (*see* later), it was decided that, if single samples were to be used, they must be obtained at the height of digestion. In breast fed infants, this is at about one hour, and, in the artificially fed, at about two hours. When the children are ill, the maximum is generally somewhat delayed. Figures in the text refer to such samples.

The samples were strained immediately through gauze and then dialyzed through collodion sacs, according to the method of Levy, Rowntree and Marriott[6]. The hydrogen ion concentration of dialysate was determined colorimetrically and expressed as pH, the indicators used being thymol blue (4·2-2·8), brom-phenol blue (3·0-4·6), methyl red (4·4-6·0), brom thymol blue (6·0-7·6). The indicators and standard solutions were made according to the directions given by Clark and Lub[2] and were tested for us, by the hydrogen ion electrode method, by Dr. Jordon-Lloyd at the Lister Institute. Repeated estimations were satisfactory and the error for the whole method should not be more than + or −0·2 on the final pH reading.

The samples removed were also tested for free hydrochloric acid by Gunzberg's reagent, and, whenever enough was obtained, titrated with N/10 soda, phenolphthalein as indicator, to give the titratable acidity. Notes were made as to the presence or absence of curds and their size.

Results.

Normal breast fed and artificially fed infants from one to nine months.

Ten children were studied in this group. They were normal, healthy infants with no discoverable defect or ailment, and all had excellent activity. None were attending the hospital, nor were they inmates of infants' homes. They did not belong to the very poor strata of society, but were clean, well cared for children. Six were breast fed, three were fed on cow's milk mixtures and one fed on a dried milk mixture. The stomach contents were examined by the fractional method and the results are shown in Table II. and Chart I. The average maximum acidity for the whole group was

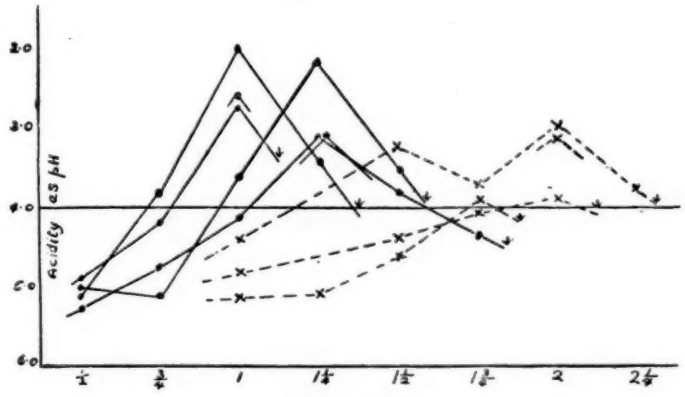
TABLE II.

Normal Children.

Sex and Age in Months.	Feed.	Time after feed that maximum acidity occurred in hours.	pH.	Titratable Acidity CC N/10 Acid %.	Free HCl Gunzberg's Test.	Remarks.
F 4	Breast	1	2·0	69%	+	Curds present
M 7	,,	1¼	2·2	59%	+	,,
M 3½	,,	1	2·9	—	+	,,
F 4	,,	1	2·7	56%	+	,,
M 3	,,	1¼	3·2	62%	0	Curds present Earlier values not obtained
F 1	,,	1¼	3·2	—	0	Curds present
M 2½	Dilute cow's milk mixture	1¾	4·0	55%	0	,,
M 6	,,	2	3·1	55%	0	—
F 8	Concentrated cow's milk mixture	2	3·0	70%	+	No curds
F 7	Dried milk mixture	2	3·9	49%	0	Very large curds

Average pH—Total ... ... 3·02.
Breast ... 2·7.
Artificially fed 3·5.

Chart I.



Time in Hours.

Curves of gastric acidity in 10 normal infants aged 1-9 months

—•— Breast Fed ---x--- Artificially Fed

↓ Stomach Empty

pH 3·02 and for the six breast fed infants pH 2·7. The highest acidity, pH 2·0, occurred in a breast fed child of 4 months one hour after feeding; this value did not represent pure gastric juice as curds were still present. In an infant of 1 month at 1¼ hours after feeding, the pH of the gastric contents was 3·2, but as there was very little in the stomach and no curds, this figure probably represents the acidity of the gastric secretion itself. Free hydrochloric acid was present in the gastric contents of four out of the six breast fed infants at some time during digestion, but only in one case was it detected in the artificially fed children. A titratable acidity of 69% N/10 acid corresponded to a pH of 2·0 in a breast fed infant and to a pH of 3·0 in an artificially fed child, showing the difference in buffering of the two feeds. Chart I. demonstrates the high maximum, the rapid rise in acidity and the rapid emptying in the breast fed and the lowered flattened curve and delayed rise in the artificially fed. A study of more artificially fed infants would probably show a less marked difference. In this connection eight artificially fed patients that were diagnosed as normal (D.P.), though attending hospital, may be considered. The average maximum pH was 3·5, the same as that for the similar true normal, but one child aged 7 months on a dried milk feed gave a maximum pH of 2·5, a value of the same order as those of the breast fed normals. These eight cases showed the same delay in attaining the maximum acidity as the other artificially fed cases.

The high true acidity values (low pH's) in the breast fed are such that peptic digestion would be active; in fact, the optimum for pepsin (about pH 2·3) was reached in two cases. The artificially fed infants also showed values in which peptic digestion would be appreciable, *i.e.*, under pH 4·0.

Underweight children.

In this group 63 children were studied. It was impossible to do a fractional analysis on all of these patients, so, when this could not be done, samples were taken at approximately two hours in the artificially fed and at approximately one hour in the case of the breast fed, and the pH of these samples taken as representing the maximum acidity. From a study of the curves in Chart I., it will be seen that this method is only an approximate one, but it is one largely used by other workers and therefore yields comparable figures.

The infants selected, except for the fact that they were all under weight and many were not gaining well, might be regarded, from the point of view of gastric function, as normal.

Table III. gives the average findings for the whole of this group and for the different classes of feeds used. The ages varied from 3 weeks to 1 year. The average pH of the gastric contents at the height of digestion was 3·94 and the range of values found at this time 1·8 to 5·3. Free hydrochloric acid was found in 12% of the cases, but, as fractional analyses were the exception, this figure was almost certainly too low. The average figures for the different feeds are extremely near together, which is surprising, in view of the current teaching on the subject.

TABLE III.

UNDERWEIGHT CHILDREN.

Number of Cases.	Nature of Feed.	Age in Months.	Average maximum Acidity as pH.	Range of maximum Acidity (pH).	Range of maximum Titratable Acidity CC N/10 Acid.	Average maximum Titratable Acidity CC N/10 Acid.
14	Breast	¾–9	4·1	2·4–4·7	16–50%	35%
13	Dilute cow's milk mixtures	2–10	3·93	2·4–5·0	28–70%	44%
8	3 parts or more cow's milk to 1 water	3–12	3·87	2·6–4·4	36–71%	55%
17	Dried milk mixtures	2–9	3·84	1·8–5·3	28–83%	53%
52	Mean	¾–12	3·94	1·8–5·3	16–83%	47%

Cases of persistent vomiting.

This group consists of seven children who suffered from persistent and intractable vomiting. Two had diarrhœa as well, but in the remaining five cases this was not present. All were artificially fed. Table IV. shows

TABLE IV.

CASES OF PERSISTENT VOMITING.

Sex and Age in Months	Feed	Time after Feed in hours	pH.	Titratable Acidity cc N/10 Acid	Free HCl Gunzberg	Remarks
F 2	Dilute cow's milk mixture	2	2·0	88%	+	Curds present
		2¼	2·0	92%	+	" "
		3	2·0	—	+	" "
M 3	Dried milk mixture	2	2·2	92%	+	" "
F 3½	" "	2½	2·9	—	+	No curds
M 4	Dilute cow's milk mixture	2	2·1	—	+	Curds present
M 4	Nestlés	1¾	3·4	—	0	Very ill
F 5½	Dilute cow's milk mixture	2	3·2	70%	+	Curds present
F 9	Dried milk mixture	2	3·8	68%	0	" "

the result of gastric analysis in these cases. The average acidity was pH 2·4, the value for titratable acidity ranged from 68 to 92% N/10 acid and free hydrochloric acid was present five times out of seven. The youngest child was 2 months old: gastric analyses were done on several occasions in this case and always gave the amazingly high acid values shown on Table IV.: at the end of three hours, curds were still present in the stomach, so that there was a markedly delayed emptying as well as a high acidity.

Ill children.

The next group consists of children suffering from acute infections and seriously ill. Thirty-two cases in all were studied, both by the fractional method and by the single estimation method; in all 108 estimations were made. Table V. gives the range and average maximum findings in the group and the various types of cases studied.

TABLE V.

ILL CHILDREN.

Number of Cases.	Disease.	Age in Months.	Range of maximum Acidity as pH.	Average maximum Acidity as pH.	Range of Titratable Acidity CC N/10 Acid.	Free HCl Gunzberg % Cases.
15	Infections Bronchitis Middle ear, etc.	2–9	6·6–3·3	4·92	21–64%	0%
11	Extreme Marasmus	2–9	5·9–3·3	4·86	25–80%	0%
5	Eczema severe	1½–7	6·7–4·0	5·14	12–45%	0%
1	Arsenical Dermatitis	10	—	3·4	68%	0%
32	Total	1½–10	6·6–3·3	4·88	12–80%	0%

A study of the curves obtained by fractional analysis is of special interest, especially when compared with the curves obtained from normal infants on the same feed. Charts II., III., IV. and V., give the results. The most striking difference is the marked lowering of the curve of gastric acidity (expressed as pH) in the sick children; this lowering is shown relative to every type of feed and is as striking in the breast fed children as in the artificially fed. The curves in the sick cases are also flatter than the corresponding normal curves. In Chart III., a composite curve from the values obtained in under-nourished infants fed on concentrated cow's milk mixtures is shown instead of a curve of normal values, as it so happened that in our series of normal infants none were fed on such concentrated mixtures. The titratable acidity is correspondingly low in these sick cases and naturally gives the same flat curves.

Gastric juice.

Before discussing the above results, it is of interest to consider the question of the gastric secretion itself. It was not possible to obtain samples of resting juice, but in certain cases samples were obtained, generally more

than 2½ hours after feeding, in which there were no curds, and which probably approximated to gastric juice, though whether a psychic secretion or the result of the stimulation of the previous feed cannot be said. The figures compare with Babbott's[1] figure of 3·3. which was obtained by lavage of the stomach. The average pH of such samples was 3·07 and free hydrochloric acid was present in practically every case. In sick children, such curd-free gastric juice was only obtained twice, when the pH's were respectively 6·7 and 4·0, but in both cases the sample withdrawn consisted largely of mucus.

COMPOSITE CURVES OF GASTRIC ACIDITY IN NORMAL AND ILL INFANTS—ALL CASES

CHART II.—Breast

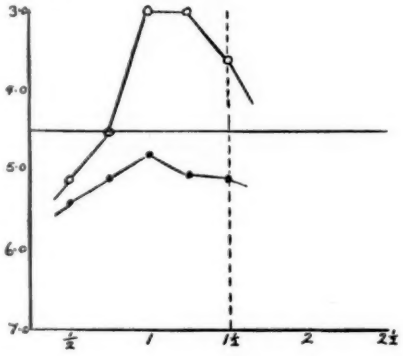


CHART III.—Concentrated Cow's Milk Mixtures

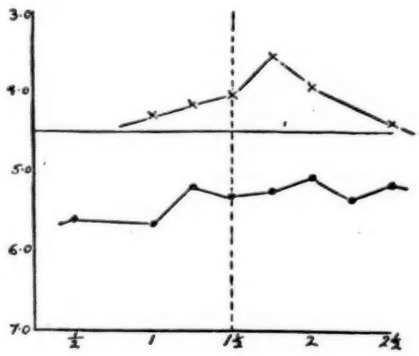


CHART IV.—Dilute Cow's Milk Mixtures

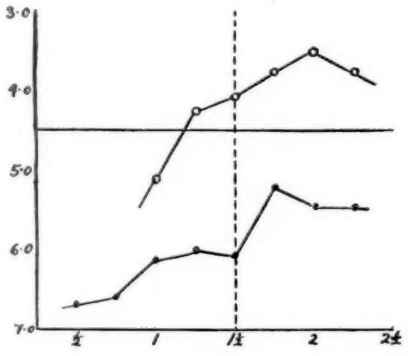
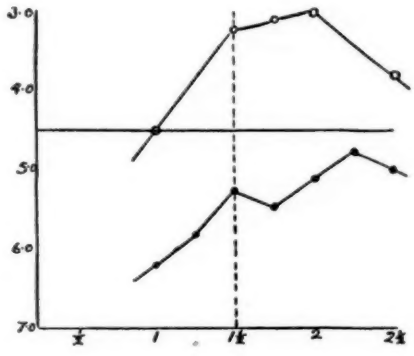


CHART V.—Dried Milk Mixtures



—o— NORMAL CASES —•— SICK CASES —x— UNDERWEIGHT CASES

DISCUSSION OF RESULTS.

Sampling.

To the two methods of sampling used in this work there are obvious limitations. The object of a fractional gastric analysis is to follow the changes in the stomach during digestion, but the fact of removing samples is in itself a disturbing factor. Again in single samples, taken at any definite

time, it is impossible to judge the stage of digestion reached. A study of the curves in Charts I. to V. shows that samples withdrawn at one hour in the breast fed normal infant will represent the condition at the height of digestion, whereas this would not be the case in the artificially fed A slight shift in time may make a great difference in value and also the error in sampling, according to Babbott[1] and Davidsohn[3], may be as great as pH 0·3. It is therefore necessary when using single samples to have a large number of cases from which to draw conclusions. Further, different workers have used different methods, therefore it is important before comparing their results to see that the samples under discussion are really comparable. Another cause of error in the samples removed is excessive salivation and also the swallowing of mucus. Davison[4] has shown the importance of these. In the cases recorded, those that had excessive salivation or nausea were excluded.

In the discussion of the fractional findings, the error in sampling is recognised, but, as the curves are remarkably similar and when repeated on the same case constant (Table VI.), they are of considerable interest and value.

TABLE VI.

REPEATED TEST MEALS.

	pH Time after feed in hours				
Case	1¼	1½	1¾	2	2¼
1	4·1	—	3·8	4·0	Empty
	4·2	4·4	3·8	Empty	—
	—	4·4	3·8	4·1	Empty
2	—	4·3	3·9	4·1	Empty
	—	4·1	4·0	4·0	Empty

Parsons[8] has pointed out that in the majority of his cases (marasmus) free hydrochloric acid occurred at some point in the curve. In our experience, to obtain such results it is necessary to take samples as near together as possible, as the rise and fall may be very rapid.

Normal values.

The cases recorded as normals would, in the light of our work, appear rather as subnormals. Babbott and his co-workers[1] recognise that their cases are not completely well, but assume that the gastric function is not affected. The group of normal children in our series shows the difference between the really active healthy infant and these subnormal hospitalised cases. Especially is this remarkable in the breast fed infant, where the average maximum acidity figure is pH 2·7. Comparing this with Davidsohn's[3] figure for breast fed children over 7 months (pH 2·92), it is seen to agree closely, but the six cases studied by us were all under 8 months, one only was 7 months, the remaining five being aged 1, 3, 3½, 4 and 4 months respectively. The maximum in the child aged 1 month was 3·2, this probably representing pure gastric juice. The shape of the curves is also remarkable. The steep rise and rapid emptying should be particularly noted.

From a consideration of these figures it is obvious that there is a greater opportunity for peptic digestion in the healthy infant's stomach than is generally thought, since pepsin is half active at pH 4·0 and fully active at pH 2·3, a value often reached in the breast fed infant. Further, in these normal breast fed cases, the stomach is empty at 1½ hours, so that on a three-hourly feed there is usually a resting period of 1½ hours before the next feed. The few normals on artificial feeds do not give such high curves, but they are too few to permit conclusions to be drawn from them. What should be remarked, however, is the delay in reaching the maximum.

The group of underweight children mentioned above corresponds to many of the normals of the literature, *i.e.*, these are subnormal children. Our findings (Table III.) are somewhat higher than those of most other workers, though Marriott's[7] figure of pH 3·75 for well breast fed children indicates a slightly higher average acidity. The fact that he obtained samples two hours after feeding in breast fed children suggests that these were not completely normal as in such the stomach would generally be empty at such a time (*see* Chart I.), but are hospitalised, *i.e.*, subnormal cases.

Another point in which the present series differs from those in literature is the similarity of the average pH on different feeds, provided the children are accustomed to the feed. Marriott[7] remarks on the increased gastric secretion to meet the need when the child is kept on a high buffer feed, but does not think that complete compensation takes place. However, a study of Table III. would suggest that in a series of comparable cases the pH approximates closely regardless of the nature of the feed. The value of each feed expressed as ounces of cow's milk was worked out for all the artificially fed infants, but no connection between either the concentration or absolute quantity of protein and pH could be determined, provided the

child had been on the same feed for some little time. A study of the titratable acidity that corresponds to the low pH values shows, what is obvious from theoretical considerations, the great increase in output of acid necessary to bring an artificial feed with a high buffer value to the same pH as a breast fed maximum (*see* Tables).

In the absolutely normal series there are not enough artificially fed cases to say whether the same would hold or not. However, the delay in obtaining the maximum will assumedly remain, as in no artificially fed infant was the maximum acidity found as early as one hour after feeding.

That it is the condition of the child rather than the nature of the feed that is of importance in determining the pH is indicated by observations on certain ill children who became progressively either better or worse while under observation. In those that went down hill, the acidity steadily decreased, while the converse occurred when the child made a steady recovery.

Sick Infants.

Vomiting children.

The series of children described shows the very high acidity associated with this condition. The cases were selected by one of us (D.P.) as being typical vomiters, though he was in complete ignorance of the values obtained (L.W.). One case, a female aged 2 months, suggests that these high acidities may be associated with pyloric spasm (cf. Parsons[8]), as the stomach was not empty at the end of three hours, and the titratable acidity was very high, 92% N/10 acid. It is not suggested that the acidity is the cause of the spasm; more likely it is the result (cf. adult cases). This was the only series of ill children examined that gave a high average maximum acidity. Davidsohn[3], in his work on the child suffering from the exudative diathesis (symptoms mentioned, vomiting and diarrhœa) mentions the high values obtained (up to 2·0). Davison[4] states that vomiting increases the acidity.

Children suffering from infections, extreme degrees of marasmus, etc.

The figures agree with those of other authors. Marriott[7], Ylppö[9], etc., state that the gastric acidity is lowered. This is marked in bronchitis and similar infections though the eczema cases (all severe cases) actually gave a lower average acidity, and it is associated with increased mucus in the stomach contents. The curves of all feeds are not only lower but remarkably flattened (*see* Charts II., III., IV. and V.).

General Discussion.

The study reported above indicates that gastric acidity in active healthy children, particularly in the breast fed, is such that active peptic digestion could take place. Free hydrochloric acid which corresponds to an acidity at

which peptic activity is at its maximum is frequently present at some stage of digestion: this is in agreement with Parsons'[8] findings in marasmic children. The average pH is lower, *i.e.*, acidity is greater, than is normally taught, if conclusions can be drawn from so few cases. Artificial feeding causes a delay in the maximum rise, apparently even when the buffer value of feed is approximately that of breast milk (1 part of milk to 2 of water). If the group of subnormal cases is considered, it is seen that compensation takes place to a very marked degree, so that, whatever the feed, the average maximum pH is the same. Similarly, the lowering of gastric acidity that takes place in ill children, except in uncomplicated cases of vomiting, is a general process and not related to one particular food. In fact, in infants as in adults, high and low acidity seem more closely related to the general condition (high acidity and good activity, low acidity and poor activity) than with the type of food or disease.

Note on the clinical application of results.

The striking difference in emptying time shown by breast fed and artificially fed infants is of significance in regard to the question of spacing infants' feeds. The stomach of a breast fed child is generally empty in 1½ hours: three-hourly feeds would, therefore, insure adequate emptying and opportunity for rest in such infants. However, in the artificially fed, whatever the nature of the feed, the stomach is not empty for two hours or more after feeding: hence, to insure complete emptying and a certain amount of gastric rest, a longer interval is necessary. Four-hourly feeds would, therefore, appear more rational (other things being equal) in the artificially fed child than in the infant on the breast.

Seven cases of persistent vomiting have been reported above; in all definite hyperacidity was demonstrated. The type of child investigated is one who, almost from birth, tends to vomit persistently. There may be no loss of weight, provided that an adequate amount of food is offered. Obstinate constipation is not present and diarrhœa is not the rule, which excludes pyloric stenosis on the one hand, and gastro-enteritis on the other. The vomit is sour with large curds and appreciable quantities may be returned. This type of case corresponds closely to that described by certain clinicians as " pyloric spasm," and they must be distinguished from cases of vomiting due to air swallowing caused by bad feeding. Clinically, they have been found to do best on small concentrated thickened feeds. It may be that the success of this therapy is partly due to the high buffer, *i.e.*, high percentage of protein of the feed, but more likely is due to the mechanical effect of the thickened feed. Since in most vomiting children the feed is lessened or weakened, the recognition of this type of case is of great practical importance.

Children suffering from an infection, or seriously ill, have been shown to have a low gastric acidity. Whatever feed these children are given, they seem quite unable to raise their gastric acidity to that point at which peptic

digestion is appreciable. This appears to us to be a very definite indication for acid feeds in such conditions. The addition of lactic or hydrochloric acid to the milk brings the stomach contents up to an acidity where peptic digestion can take place. Peptonising the milk would also circumvent this, but has not proved so practicable.

Summary.

1. Normal healthy infants under one year have an average maximum gastric acidity of pH 3·02 for all feeds. Breast fed infants have a higher acidity, *i.e.*, 2·7, and in most cases those over one month old show free hydrochloric acid at some time during digestion.

2. The pH of 2·7 is such that active peptic digestion could take place.

3. The gastric emptying time in breast fed infants is more rapid than in the artificially fed.

4. Slightly underweight children have a lower acidity than true normals, though there is no obvious gastric defect. The average pH is nearly the same for the different feeds, indicating a compensatory increased gastric secretion, where infants are fed on high buffer feeds.

5. Infants suffering from persistent vomiting (not ruminators) have a high gastric acidity.

6. Ill children have a lowered gastric acidity.

7. The gastric findings in infants, as in adults, seem more closely associated with the general condition of the child than with any particular feed or disease.

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CALCIUM ABSORPTION IN RELATION TO GASTRIC ACIDITY
(A Study of Rickets).

BY

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Many workers have put forward the hypothesis that, since calcium salts are soluble in hydrochloric acid, increased gastric acidity will increase the calcium absorption and hence the supply to the body. The converse hypothesis has also been advanced to account for the mechanism of the failure of the calcium supply of the body in rickets. Faber[2], in his argument in support of hydrochloric milk, puts forward this increased solubility of the calcium. The same argument has been used by Shaw and Williams[13] and Gleich[5] for Marriott's lactic acid milk[10]. Telfer[15] has made experiments on dogs, showing the increase in soluble calcium salts in the stomach of dogs fed with the addition of hydrochloric acid. Jones[7] has recorded three cases of rickets treated with hydrochloric acid milk, but as they were uncontrolled and two had also had other treatment, it is difficult to make any deduction from her results. Other workers (Shohl and Sato[14]) have shown that the addition of acid to the diet causes increased loss of base, especially calcium, from the body.

As the calcium absorbed from the food cannot be marked, it is impossible to say in a case of negative balance that so much of the calcium has not been absorbed and then excreted into the gut again, but, if a larger percentage is excreted through the urine, it is fair to argue that there has been an increased absorption, though finally the total excretion may be increased.

The following statements are generally accepted as correct. In active rickets, the retention of calcium is decreased and the balance may be negative (Holt[6] [11], and Glasgow school[3]). When treated by either cod-liver oil, or ultra-violet light, the retention is increased (Orr, Holt and others[11]). All calcium salts that are soluble in an acid medium are available as a source of calcium for the body (Steenbock and others[16]).

Bearing these facts in mind, the following research was designed to see if it were possible to correlate a decreased acidity with a poor absorption and retention of calcium and *vice versa*. The work was divided into two parts:—

1. The effect of giving acids, or acid-forming salts, on the calcium balance.

2. The relationship, if any, between the changes in calcium retention that occur in the healing of rickets and any change in gastric acidity.

Estimations of serum calcium and the inorganic phosphates of the blood were also carried out on the same patients.

Methods.

In estimations of gastric acidity, no definite test meals were given, but the stomach contents were removed and examined after the ordinary feed that the infant was taking. A fractional examination was made in every case. The samples removed were strained through gauze and then dialysed through collodion sacs, according to the method of Levy, Rowntree and Marriott[8]. The hydrogen ion concentration of the dialysate was determined colorimetrically and expressed as pH. The samples removed were also tested for free hydrochloric acid by Gunzberg's reagent and, whenever enough was obtained, titrated with N/10 soda, phenolphthalein as indicator, to give the total free and combined acidity.

For the calcium balance estimation, the child was placed on a metabolism bed after a period on a constant diet and the fæces and urine collected over periods of four days. The food, some milk preparation, was made up in bulk each day and samples estimated daily. In this way, errors arising from inaccuracies in making up the formula were avoided, as the actual mixture taken was analysed. The fæces and feeds were carefully dried, weighed, ashed and the calcium estimated by McCrudden's[9] method, and the calcium in the urine estimated by Shohl and Pedley's[15] method. The greatest care was taken to avoid loss in the collecting of the stools and urine.

At the same time, blood analyses were made for serum calcium (Tisdall's method[19]) and blood phosphates. The phosphate values were determined by Dr. Robison of the Lister Institute and it is through his kindness that we are permitted to use his figures. The blood analyses were used to confirm the X-ray diagnosis of rickets and cases giving a normal blood picture were not considered active. It is not meant to enter into any theoretical consideration of the value of these determinations, but this definition of active rickets was taken, as it was hoped that such cases would give the most helpful findings.

Investigation of Calcium Balance in Children Receiving Acid Feeds.

This group consists of two children who were fed on hydrochloric acid milk, one child that received ammonium chloride for tetany and three children who were fed on lactic acid milk. In every case, the child was on a fixed diet for at least a week before the first period (four days) on the metalbolism bed. The acid, or salt, was then added to the diet, and, after a period to allow the child to come into equilibrium with the new feed, the metabolism period was repeated. The results of the two metabolism periods and the blood findings are set out in Table I.

TABLE I.

Calcium Balance on Acid Feeds.

Sex and Age in months.	Body Weight in kilogms.	Feed	Weight of dried fæces grammes per day	CaO gms. per kilo of Body Weight per day			% Retention	Serum Calcium mgms. Ca per 100c.c.	Inorganic Phosphates mgms. P per 100 gms. whole blood	Maximum Gastric Acidity as pH	Positive Gunzberg Free HCl.
				Intake	Output	Retention					
M 12	7·67	Milk mixture ...	10·4	0·173	0·125	+0·0485	+28	10 4	—	3 9	0
,,	7·57	Same plus dil. HCl ...	21·1	0·152	0·178	−0·026	−17·4	10·5	—	2·5	+
F 24	9·1	Milk mixture ...	35·4	0·125	0·089	+0·036	+28·7	10·0	4·45	4·0	0
,,	9·47	Same plus dil. HCl ...	22·0	0·123	0·154	−0·031	−25·1	10·3	3·83	2·5	+
M 12	6·0	Milk mixture ...	7·3	0·167	0·093	+0·075	+44·6	6·1	3·64	4·1	0
,,	6·1	Same plus Am. Chloride	11·5	0·175	0·188	−0·013	− 7·5	6·4	—	5·7	0
F 5½	3·6	Milk mixture ...	6·9	0·212	0·126	+0·086	+53·9	—	—	4·4	0
,,	3·8	Same plus Lactic Acid	6·3	0·241	0·158	+0·082	+34·2	—	—	3·1	0
M 3	5·0	Milk mixture ...	5·6	0·156	0·106	+0·0505	+32·4	—	—	4·0	0
,,	5·2	Same plus Lactic Acid	6·0	0·184	0·160	+0·024	+13·2	—	—	3·2	0
M 3	4·0	Milk mixture ...	10·0	0·239	0·1595	+0·080	+33·3	—	—	4·2	0
,,	4·0	Same plus Lactic Acid	6·0	0·192	0·114	+0·078	+40	—	—	4·0	0

Both the children receiving hydrochloric acid milk were previously in a low positive calcium balance,—percentage retentions of 28 and 28·7 and retentions per kilo of +0·048 and +0·036 grammes calcium oxide respectively. Hydrochloric acid was added according to Faber's formula to the milk, *i.e.*, one ounce of 1/10 normal hydrochloric acid to four ounces of milk. After four days on the same to bring the child into equilibrium with the feed, the calcium balance was again determined. In both cases there was a very definite negative balance, −17·4% and −25·1% retention, or −0·026 and −0·031 grammes calcium oxide per kilo. In the first case, the daily output of dried stool was increased, but the converse took place in the other child. The gastric acidity rose, maxima, before HCl, pH 3·9 and 4·0 respectively and after HCl, pH 2·5 in both cases. Free hydrochloric acid was present in both in the second period.

As regards the blood changes, in the first case the serum calcium rose from 10·4 to 10·5 milligrammes per 100 c.c., a rise within the limits of error of the method, and in the second case from 10 to 10·3. The inorganic phosphates in the second case fell from 4·45 to 3·85 mgms. per 100 gms. of blood.

In brief, both cases showed a markedly negative balance, but the serum calcium was not lowered in either, but, on the contrary, slightly raised (all normal values). The inorganic phosphates were lowered. The question of greater excretion through the urine was not determined as there was a loss in the male case and as the second was a female, the urine was frequently mixed with the stool. On the occasions when it was collected separately, there was only a very small proportion of the total calcium excreted in the urine. A large part of the increased calcium excretion must therefore be through the gut.

The case on ammonium chloride (30 grains for the first day and 15 grains for three days and while on the bed) showed a similar negative balance (*see* Table I.). The retention changed from +44·6% to −7·5%, or in grammes from +0·075 grammes calcium oxide per kilo to −0·013 grammes per kilo. This case was complicated by constipation in the first period, the total dry fæcal weight per day being respectively 7·3 and 11·5 in the two periods. The gastric acidity did not increase, but rather decreased, due apparently to increased secretion of mucus. The serum calcium again rose slightly from 6·1 to 6·4 mgms. The phosphates were not determined.

The three cases treated by Marriott's lactic acid milk, *i.e.*, 60 minims B.P. lactic acid added drop by drop to 1 pint of cold milk, did not show anything like such a marked change in their calcium balance (*see* Table I.). The first two cases were satisfactory, as the weight of fæces per day was very constant in the periods. The actual intake of calcium in both cases increased during the lactic acid periods and yet in both cases there was a definite drop in the retention values,—no negative balance, but a smaller retention, from 54% to 34% and from 32% to 13%, *i.e.*, from +0·0864 to +0·0821 and from

+0·0505 to +0·0242 grammes calcium oxide per kilo respectively. In the third case, in the second metabolism period, the child was seedy and off its food and the percentage retention was greater, owing to the much smaller intake, though the absolute retention in grammes was smaller. The gastric acidity was increased in every case, but in none to such an extent as with the hydrochloric acid milk, and no case showed free hydrochloric acid.

The cases on acid feeds therefore all showed a negative calcium balance, or a less positive one, though in every case the gastric acidity, and thus presumably the amount of calcium in solution, was increased.

Cases of Rickets.

Very few cases of rickets were seen during the period of study, in fact, only eight definite cases (Table II.), all of whom were on milk feeds. It

TABLE II.

Number of Cases.	Condition.	Age in Months.	Range of maximum Acidity as pH.	Average maximum Acidity as pH.	Range of Titratable Acidity CCN/10 Acid	Presence of Free HCl Gunzberg Number of Cases.
8	Active Rickets	8—24	5·4—3·6	4 5	26—40%	0
6	Healing Rickets	8—21	4·8—2·6	3·4	40—90%	2

is seen that the average acidity increases when healing (X-ray) is taking place, the maximum acidity before healing being pH 4·5 and during healing pH 3·4.

Seven of these eight cases were studied from the point of view of their calcium metabolism and four were followed through from the active stage to a stage of healing. The diet of each was constant throughout the entire period of observation. The chemical findings are set forth in Table III. The cases will first be considered separately.

Case I. D. G., female, aged 20 months.—A severe case with typical X-ray findings. Two metabolism periods showed that the calcium balance was negative, —0·003 grammes calcium oxide per kilo. The inorganic phosphates of the blood had the extreme values of 2·6 mgms. and 1·9 mgms. per 100 gms. at the end of the two periods respectively, and the serum calcium of 8·0 and 7·1 mgms. per 100 c.c. The gastric acidity had a maximum of pH 3·6 and 3·8 for the two periods. After treatment with cod-liver oil till marked signs of healing (X-ray) were present, a third period on the metabolism bed showed she had now an extremely good retention, +0·120 grammes calcium oxide per kilo, and the retention percentage was very high, +60·7%. The calcium excreted through the urine had changed from a minute trace to about 0·5% of the total output. The inorganic phosphates of the blood had risen to 5·31 and the serum calcium to 10·1. The gastric acidity had risen from pH 3·6 to a maximum now of pH 2·0 with free hydrochloric acid. The child had changed from a miserable limp object to a bouncing irrepressible creature.

TABLE III.

Calcium Balance and Gastric Acidity in Cases of Rickets.

Sex and Age in months.	Body Weight in kilogms.	Feed.	Weight of dried fæces grammes per day.	CaO gms. per kilo of Body Weight per day.			% Retention.	Serum Calcium mgms. Ca per 100 cc Serum.	Inorganic Phosphates mgms. P per 100 gms. of whole blood.	Maximum Gastric Acidity as pH.	Free HCl Gunzberg.
				Intake.	Output.	Retention.					
1. F. 20. Active Rickets 28.1.25	5·68	Cow's milk	14·8	0·189	0·1915	−0·003	−1·5	8·0	2·6	3·6	0
On Patent Extract of Cod-liver Oil 25.2.25	5·85	Rusks	17·6	0·193	0·197	−0·003	−1.8	7·1	1·9	3·8	0
On Cod-liver Oil—healing 23.3 25	6·3	Orange juice	16·4	0·198	0·077	+0·121	+60·7	10·1	5·31	2·0	+
2. M. 12. Tetany Active Rickets 1.4.25	6·0	Cow's milk	7·3	0·1675	0·093	+0·075	+44·6	6·1	3·64	4·1	0
On Cod-liver Oil—healing 6.5.25	6·36	Orange juice	13·1	0·172	0·083	+0·089	+51·6	10·0 11·0	—	3·1	0
3. F. 9. Active Rickets Latent Tetany 13.4.25	7·7	Cow's milk Egg Benger's	16·2	0·192	0·177	+0·015	+7·7	6·2 6·4	—	4·8	0
Spontaneous healing ... 11.5.25	8·4	Orange juice	11·4	0·160	0·091	+0·069	+42·5	8·8 10·6	—	3·8	0
4. F. 12. Active Rickets 16.3.25	6·7	Cow's milk Egg Broth	11·5	0·082	0·052	+0·030	+36·7	9·6 8·6	3·27 2·42	5·4	0
On Cod-liver Oil—healing 20.4.25	6·8	Orange juice	8·0	0·155	0·067	+0·088	+56·9	9·0	—	4·8 (once only)	0

Case II. Male, aged one year.—This case did not show a negative calcium balance when admitted with rickets (X-ray) and tetany, and the retention per kilo (+0·075 grammes calcium oxide) was not low. This metabolism period was not very satisfactory, however, owing to constipation, but could not be repeated as it was essential to treat the child. The maximum gastric acidity was pH 4·1. The inorganic phosphates of the blood were 3·64 mgms. per 100 gms., but the serum calcium was only 6·1. The case was first treated with ammonium chloride as described above, and then with cod-liver oil, and did well, but not as remarkably as the previous case. When healing was marked (X-ray), a further balance period gave a slightly increased calcium retention, which was now good (+0·089 grammes calcium oxide per kilo). The gastric acidity rose to pH 3·1, but free hydrochloric acid was never detected.

Case III. Female, aged nine months.—A case of moderately severe X-ray rickets with latent tetany. The balance was not negative on admission, but very low (+0·015 grammes calcium oxide per kilo). The serum calcium was 6·3 mgms. per 100 c.c. The maximum gastric acidity was low, pH 4·8. Slow spontaneous healing took place (light in ward) and a further balance period showed a calcium retention of +0·069 grammes calcium oxide per kilo. The serum calcium rose to 8·8 and then 10·6 mgms. per 100 c.c. and the maximum gastric acidity to pH 3.8. The clinical condition improved considerably, but was better later when treatment was added.

Case IV. Female, aged one year.—This case was of interest as it gave a marked X-ray picture and clinically the child was very ill; anæmia, fits (not tetany), and extremely poor muscle tone. The balance period showed a low positive balance +0·030 grammes calcium oxide per kilo. The inorganic phosphates of the blood were 3·27 at the beginning and 2·42 mgms. per 100 gms. just after the first metabolism period, and the serum calcium was 9·7 and 8·6 mgms. per 100 c.c. respectively for the same two periods; yet a few days later X-ray healing was clear, and a week later there was a marked improvement in the X-ray picture. The patient was treated with cod-liver oil and healed (X-ray) very well and rapidly. A metabolism period then showed a calcium retention of +0·088 gms. calcium oxide per kilo, and the serum calcium rose to 9·0 again. The gastric acidity findings were remarkable; during the first period the maximum was pH 5·4, during the second period one reading of pH 4·8 was obtained, otherwise the pH values were never below 5·6. Test meals were repeated time after time, but high acidity values could not be obtained. It is to be noted here that. although excellent X-ray healing was taking place, the child was still miserably ill, anæmic, having fits and very flabby.

Discussion of Results.

The cases on hydrochloric acid, or acid-forming salts, appear quite sharp cut. The addition of a strong acid, such as hydrochloric, to the diet, even in the quantities used by Faber[2] and other clinicians, produces a marked lowering of the calcium retention,—in fact, in our cases, a negative balance,—and the same remarks apply to ammonium chloride.

Various authors, engaged in the study of acid base balance, have reported findings that are pertinent to the question under consideration. Shohl and Sato[14] gave 250 c.c. of N/10 acid a day to two infants 9 months old (our cases had 170·4 c.c.) and found an increased calcium output both in stools and urine, though the balance did not become negative (they gave 1·031 and 0·775 grammes calcium oxide respectively compared to our 1·148 and 1·166 grammes calcium oxide). Sawyer, Baumann and Stevens[12] produced an acidosis by giving fats and got a marked calcium loss as a result. Givens and Mendel[4] gave hydrochloric acid and thereby increased urinary excretion of calcium. Stewart and Haldane[17] have shown that, by taking either ammonium chloride or calcium chloride, the excretion of calcium by

the urine is increased and also that the normal serum calcium value is slightly raised, a fact they attribute to the concentration of serum colloids in acidosis. Our results confirm the above mentioned authors.

Further, the investigation with lactic acid milk also indicates that such an acid, though probably entirely destroyed in the body, upsets the acid base equilibrium and leads to a slight loss of base (cf. Blatherwick and Long[1]). In view of these findings, it is difficult to understand how the addition of hydrochloric or lactic acid to the diet of a rachitic infant can help the process of healing should this be dependent on, or run parallel with, an increased calcium retention.

Telfer[18], working on calcium metabolism in rickets, showed that, in dogs, a greater proportion of the calcium salts of the food were in solution at a stated time after feeding when hydrochloric acid was given with the food, and therefore assumed that the absorption of calcium would be better when gastric acidity was high. This is probably correct, but the acidosis produced by giving hydrochloric acid accounts for the great loss of calcium and other bases (*see* Shohl and Sato[14]), found in infants fed on hydrochloric acid milk.

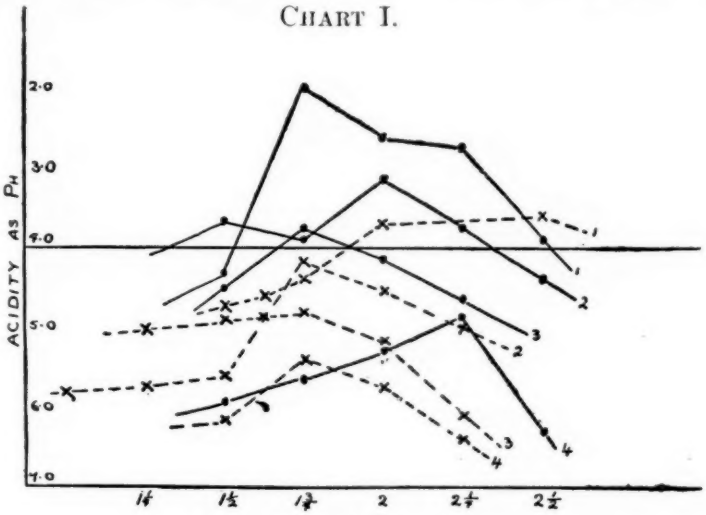
The good results obtained clinically on hydrochloric acid milk (Faber[2] and others) probably depend on other actions, such as the control of diarrhœa with good soap stool formation, and the fact that in some cases the intake of calcium probably is sufficient and the dose of hydrochloric acid possibly low enough to prevent an actual negative balance. But, in view of our findings, it would seem unwise to give hydrochloric acid milk over long periods to either rachitic or normal children.

The fact that increasing the acidity of the stomach by adding acids does not lead to an increased retention, but the converse, does not disprove the theory that the poor retention in rickets is due to the low gastric acidity (Zucker and others[20]), as the disturbing factor of adding a foreign acid may neutralise the beneficial effect of the increased absorption. If by other means the gastric acidity could be raised and shown to be associated with an increased calcium retention, this would be suggestive evidence in favour of the hypothesis. The known action of cod-liver oil, or light, in causing healing and an increased retention of calcium in cases of rickets led us to use such cases in looking for any relationship between changing calcium retention and changing gastric acidity.

The four cases studied must be examined in detail. The first case looked at alone would apparently prove the hypothesis, healing and an enormously increased calcium retention being associated with a marked change in gastric acidity, free hydrochloric acid being present in the healing state. The serum calcium was also increased. The second and third cases also support the theory, but the fourth case must be considered separately. The calcium retention was low, +0·030 grammes calcium oxide per kilo, and the gastric acidity extremely low, maximum reading pH 5·4. The X-ray plates showed remarkably good and rapid healing and the retention rose

to +0·088 grammes calcium oxide per kilo. In this second period, except for one curve (shown on chart), the gastric acidity curves were lower than in the preceding untreated period. The maximum acidity, pH 4·8, was the same as the maximum reading in Case 3 (untreated), when the retention was only +0·015 grammes calcium oxide per kilo. Chart I. gives the curves of these cases before and after treatment. In the face of such curves,

CHART I.



Curves of Gastric Acidity n 4 Cases of Rickets.

it is difficult to believe that the increased retention is directly dependent on the increase in gastric acidity and, therefore, on the solubility of the salts, more especially when it is noted that Case 4 healed (X-ray) most rapidly, in spite of the very low level of gastric acidity.

A consideration of the gastric findings in other cases shows that infants suffering from an infection or serious illness (except persistent vomiting) have a low gastric acidity, but the majority of such cases do not develop rickets, though the infection, or illness, may be of long standing, and should therefore lead to a poor calcium supply, did this depend on a low gastric acidity.

In a previous paper a relationship between body tone and gastric acidity in infants has been suggested; this is particularly well illustrated in the rachitic Cases 1 and 4 in the present series. Case 1 came into hospital unable to stand and very flabby, she went out " bouncing " or, more technically, with extremely good activity. Case 4 came in and went out a miserable flabby child, though healed of her bony rickets. In fact, in infants as in adults, it is probably correct to say that good tone goes with good acidity and *vice versa*. X-ray examination would confirm this.

Hence, though the cases of rickets show an increased gastric acidity when healing, we would associate this rather with general increase in tone than in any way with the healing process. Doubtless an increased acidity

does increase the solubility of the salts of the diet, but this is not the limiting factor in the supply of calcium to the body, or its retention, as the body can and does obtain an adequate supply of calcium on extremely low levels of gastric acidity.

SUMMARY.

1. Calcium retention was decreased, the balance was negative, in infants fed on hydrochloric acid milk, or treated with ammonium chloride: in the first case, the gastric acidity was greatly increased and the converse occurred with ammonium chloride.

2. Lactic acid milk feeding led to a slightly increased loss of calcium. The gastric acidity was raised.

3. In healing rickets, the retention of calcium was increased, but the increase in gastric acidity which occurred in the majority of cases did not run parallel with this increased retention, but rather with the general condition of the child.

4. Gastric acidity does not appear to be a limiting factor in the supply of calcium to the body.

We are indebted to Dr. Eric Pritchard, Director of the Hospital, for permission to work in the Research Laboratory. The expenses of this research were paid by the Medical Research Council to which we offer our sincere thanks.

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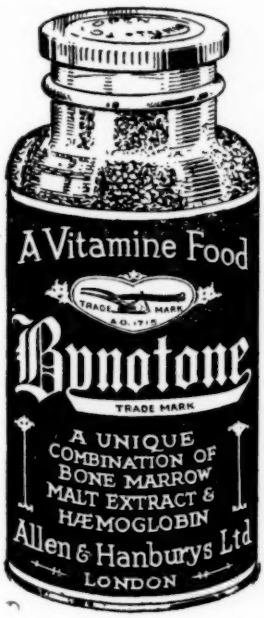

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A CONTRIBUTION TO THE STUDY OF THE CAUSATION OF FŒTAL DEATH*

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During the last few years, more attention has been paid to what has been, beforetime, a much neglected branch of pathology—the subject of fœtal and neo-natal death. Its importance is obvious. The yearly wastage of fœtal life assumes enormous proportions; nor is this all. The death rate during the first week of life is still very high, and it is to be presumed that some, at any rate, of the factors causing fœtal death may be instrumental in the production of this high death rate, and that a sounder knowledge of fœtal pathology and its treatment would not only reduce the number of still births, but also be associated with a lowered infantile mortality.

Classification of the causes of fœtal death in this series. It is very difficult to classify the causes of fœtal death; indeed the very term ' still birth ' and even ' fœtus ' are ill-defined in the literature. The word ' fœtus ' should not be used indiscriminately, and is not interchangeable with the words ' child ' and ' infant.' The term covers a definite period of existence extending from the end of embryonic life to the time when the tissues are ærated by means of its own respiratory efforts. Thus the fœtus has an extra-uterine existence. This is usually very short, but in some instances (*e.g.*, after Cæsarian section) there may be a prolonged interval before respiration is established. It is then obvious that the term ' still birth ' must be confusing because it involves more than one entity. The fœtus may die in utero, and later be delivered macerated; it may be killed during labour, or it may be born alive with the heart beating and fœtal movements occurring, and yet its pulmonary respiration may not be established. To each of these cases the term ' still born ' applies, yet, as regards their causation and pathology they are widely different. This subject was fully discussed in 1914 by Ballantyne who suggested a solution of the problem by the additional use of the word ' dead birth.' Thus the use of the term ' still birth ' would be restricted to the fœtus born alive and dying before the establishment of pulmonary respiration, and the term ' dead birth ' reserved for the fœtus born without signs of life.

*The material of this paper is derived from 160 autopsies performed at the Jessop Hospital for Women, Sheffield, on still-born viable fœtuses, or on children dying within seven days of birth, forming a consecutive series, from March, 1923, to March, 1925. My thanks are due to the Honorary and Resident Staff of the Jessop Hospital for their valued help during that period.

Even when definition is made clear, the problem of classification of the causes of fœtal death will still be hedged about with difficulties, not only because of great ignorance on such subjects as the transference of disease to the fœtus in utero, but also because of the many factors brought into play in any one case. For example, at an autopsy, it may be found that the fœtus has extensive intra-cranial hæmorrhage, which is the ultimate cause of death. But we may find that the child was premature and the mother had placenta prævia, for which version was performed. It was presumably during these manipulations that the child was injured. It has been considered in such cases that the actual cause of death was the cerebral hæmorrhage, the predisposing factors being the premature separation of the placenta and the prematurity of the child, which rendered its tissues more likely to damage. In any classification, therefore, there must be considerable overlapping of the various categories, maternal and placental states predisposing in many instances to the fœtal condition found at autopsy.

In the present series of cases there were, in all, 160 post mortem examinations made. They form a consecutive series of still-born viable fœtuses, or children dying within seven days of birth (Table I.).

TABLE I.

CAUSES OF FŒTAL DEATH IN 160 CONSECUTIVE AUTOPSIES ON STILL-BORN VIABLE FŒTUSES.

MATERNAL STATES.	No. of Cases.
Albuminuria	7
Eclampsia	9
Nephritis and Endocarditis	1
PLACENTAL STATES.	
Placenta prævia	22
Retro-placental hæmatoma	10
Placental infarction	3
FŒTAL STATES.	
Traumatism at birth	105
Fœtal infections	14
Fœtal anomalies	10

In this classification, there is an overlap of 21 cases where morbid maternal or placental conditions caused or complicated the state of the fœtus found at autopsy.

FŒTAL DEATH DUE TO FŒTAL CONDITIONS.

It is proposed to omit the first two categories, as here set out, and to deal only with the fœtal conditions found. These may be sub-divided into three groups:—

(I) Traumatism at Birth. (1) Craniotomy. (2) Hæmorrhages of the new-born.

(II) Fœtal Infections.

(III) Fœtal Anomalies.

I.—TRAUMATISM AT BIRTH.

It is an aphorism that many more fœtuses owe their death to the complications of delivery than to maternal or fœtal disease. Figures here (105 out of 160 or 66%) speak for themselves. It must be remembered, however, that in this classification we are dealing only with the ultimate cause of death, and the predisposing causes (as, for example, placenta prævia, or contracted maternal pelvis) must be brought into consideration.

A second aphorism may be propounded: the fatal results of traumatism are due to hæmorrhage. It is, therefore, with the pathology and ætiology of hæmorrhages of the new-born that we are now concerned.

1. Craniotomy.

I do not propose to deal with these cases in detail. In the majority of cases, the gross trauma has destroyed those parts of the fœtus which are most interesting from a pathological standpoint, namely, the cranium and its delicate contents. In most cases petechial hæmorrhages were met with in other parts of the body. Nothing else of interest has emerged during the examination of the bodies of these fœtuses. Reduction in the number of cases of craniotomy can come by no help from the pathologist, but only from improvement of what Holland calls 'the strategy and tactics of obstetrics.'

2. Hæmorrhages of the New-Born.

The pioneer work on this subject was published by Spencer[18] in 1892, following the writings of Sarah McNutt[11]. He gave a detailed account of a consecutive series of 130 autopsies on fresh, mostly still-born fœtuses, and drew some new and remarkable conclusions. Amongst these he stated that visceral hæmorrhages more commonly followed breech delivery than cephalic, and that cerebral hæmorrhage is more frequently found in still-born fœtuses delivered by forceps than in those born naturally by the head or breech. He realised that these hæmorrhages, when not immediately fatal, may be followed by the gravest consequences. He found intra-cranial hæmorrhages in 40·7 per cent. of cases, and noted that, in a certain number of these, bleeding had occurred into the falx and tentorium, but actual tears of the meninges were not mentioned. This omission was due presumably to the method of opening the skull, for it was not till, in 1910, Professor Beneke[3] introduced a new method that it was possible to expose the tentorium and falx adequately.

Classification of Hæmorrhages.

In all but 6·9% of cases, hæmorrhage of some degree had occurred. This is an astounding figure until we realise that in 50% hæmorrhage was petechial in type and not *per se* the cause of death:—

TABLE II.

TYPES OF HÆMORRHAGE FOUND.

	Cases.	Per cent.
(i) Petechial hæmorrhage only	80 ...	50
(ii) Gross intra-cranial hæmorrhage ...	60 ...	37·5
(iii) Gross visceral hæmorrhage	9 ...	5·6
(iv) No hæmorrhage	11 ...	6·9
	160 ...	100

(i) *Petechial Hæmorrhages.*

It is seen that these were almost constant in still-born fœtuses. They varied considerably in number and in size; in some cases they were a most obvious lesion when the body was opened, in others they were found only on careful examination. They were much commoner in the thoracic viscera than in the rest of the body, the usual sites being (a) beneath both visceral and parietal pleura, and (b) beneath the visceral pericardium, especially that covering the upper part of the right ventricle. Frequently also they may be found in the cranium, between the two layers of the falx and of the tentorium. Less commonly, they are also seen in other viscera, as the thymus, liver, and kidneys. In most of the cases, marked congestion of the viscera is associated with them.

These hæmorrhages are found in widely different circumstances, the two cases where the hæmorrhages were most numerous occurring respectively in placenta prævia and prolapse of the cord. The only factor that the cases show in common is the degree of anoxæmia, and these small hæmorrhages may be presumed to correspond to the Tardieu's spots found in true asphyxia.

(ii) *Gross Hæmorrhages (Visceral and Intra-Cranial).*

Gross hæmorrhages are an extraordinarily common cause of fœtal and neo-natal death. It is probable, too, that the effects do not end here, but are the cause of disabilities which may persist through life.

We have met with gross hæmorrhages 69 times, and of these, 60 showed the results of intra-cranial trauma. The evidence of trauma is found in tears of the meninges, and the devastating effects are due to hæmorrhage. In a certain proportion of these there were tears of the falx cerebri and gross hæmorrhages of the thorax and abdomen, but compared in

frequency with tears of the tentorium, these are rare. Tears of the tentorium were found in 58 cases (exclusive of craniotomies)—a percentage of 36·25 of the total number in the series.

The results of other observers are as follows:—Warwick[21], in a series of 36 still births and neo-natal deaths, found 50 per cent. showed intra-cranial hæmorrhage. Schafer[13] found this percentage to be 20 in a series of 680 autopsies upon newly-born infants. Ehrenfest[7] claims that tentorial ruptures occur in 30 to 40 per cent. of cases of fœtal death and deaths occurring soon after delivery. Holland[9] [10] found tears of the tentorium to be present in 48 per cent. of fresh still-born fœtuses.

Tearing of the tentorium alone cannot cause death, but in 57 cases out of the 58 autopsies where this type of meningeal tear was found, hæmorrhage had occurred. For purposes of comparison, the amount of blood extravasated was graded empirically as ' little,' ' moderate ' or ' much.' Much blood was found in 30 cases, a moderate amount in 19, and little in 8, but it is to be remembered that in many of the cases where the bleeding has been designated as ' little ' in quantity, there was accumulation of blood beneath the tentorium, where even a small increase of pressure may be fatal.

It is seen, then, that tears of the tentorium may be regarded as an index of intra-cranial hæmorrhage, and their ætiology must be the same. The same force which tears the meninges produces the hæmorrhage which so often proves fatal. It follows that the anatomy of the dural septa and the part that they play during labour is of outstanding importance.

Anatomy of the Dural Septa.—The tentorium (according to Cunningham) is a crescentic partition of dura mater which forms a membranous covering to the posterior cranial fossa. The cranial dura mater is composed of two layers intimately connected with each other in most regions of the cranium. Along certain lines these layers separate so as to form channels lined with endothelium. These are the blood sinuses. Thus the posterior border of the tentorium from the internal occipital protuberance to the postero-inferior angle of the parietal bone encloses the lateral sinus. Along the superior border of the petrous bone it encloses the superior petrosal sinus. At the junction of the tentorium and falx, the two membranes blend to form a strong band which Holland has called the ' white line.' Along this attachment is enclosed the straight sinus, and at the level of the internal occipital protuberance, where the superior longitudinal sinus ends in joining the lateral sinus, is the torcula herophili, the greatest sinus of all.

The Dural Septa during delivery.—The dural septa are normally in a state of rest, but when labour begins, alterations in their tension are inevitable owing to the nature of their attachment to the cranial bones.

Holland has put forward the theory that the septa should be regarded ' as stays to the cranial bones, like stays to a mast,' exercising a protective function against excessive and dangerous alterations in shape of the fœtal head. He believes that the special strengthening bands contained in the septa are specially arranged so as to withstand the stress likely to fall upon cranial contents during moulding of the head. The arrangement of these fibrous bands is interesting; when the fœtal head is opened by Beneke's method, they can be seen shining through the dural septa radiating ' like spokes of a wheel.'

Tears of the Dura and their Ætiology.—The site of predilection for dural tears occurs on either side the tentorium just where the fibres of the falx diverge to form its upper blade. The tear may be complete or incomplete.

unilateral or bilateral. I found the falx torn in 12 instances only, always in association with tears of the tentorium.

There are two factors which predispose to tears of the dural septa during delivery: (1) Prematurity; (2) Syphilis. Of the 58 fœtuses exhibiting torn septa, 17 or 29·3% were premature. F. Browne[4] states that ' The tissues of fœtuses of 7, 7½ and 8 months, are too fragile to pass uninjured through the birth canals,' and agrees that syphilis renders the fœtal tissues more friable.

The exciting cause, however, may be found in cranial stress during delivery, so that the method of delivery in these cases is of importance.

TABLE III.

PRESENTATION IN 58 CASES OF TORN DURAL SEPTA.

	No. of Cases.
HEAD PRESENTATION:	
(1) Without forceps	13
(2) With forceps	17
BREECH PRESENTATION:	
(1) Primary breech	11
(2) After version	17

Of the 30 cases of head presentation, it is seen that 13 times forceps were not applied, but only twice can intra-cranial trauma be said to have been caused during normal delivery of a full-term child. An analysis of the 13 cases is given (Table IV.)

TABLE IV.

Prematurity of the fœtus	4 cases.
Prolonged labour	2 ,,
Precipitate labour	2 ,,
Contracted pelvis	3 ,,
Normal delivery—full-term child	2 ,,
	13 cases.

Forceps were applied 17 times, the indications for their use being as in Table V.

TABLE V.

Contracted pelvis	5 times.
Placenta Prævia	2 ,,
Prolapsed cord	2 ,,
Occipito-posterior presentation	6 ,,
Primary uterine inertia	2 ,,
	17 times.

Breech deliveries resulted in tearing of the tentorium in 28 cases. In 11 of them the presentation was primarily by the breech, and in 17 breech delivery was the result of version (for placenta prævia 13, for transverse lie 4).

From these figures it is seen that, though tears of the tentorium may occur during the course of a normal vertex delivery, they are uncommon. Prematurity predisposes to the fœtal danger, but the determining causes may, for practical purposes, be divided into (a) excessive stress applied to the fœtal head during delivery (as in cases of contracted pelvis, forceps delivery), and (b) normal stress applied too rapidly (as in precipitate labour).

E. Holland, in considering his series of torn tentoria, came to the conclusion that the particular force required to tear the tentorium was applied in the antero-posterior diameters, *e.g.*, sub-occipito bregmatic. Decrease in this direction necessitates compensatory increase in the vertical height. That part of the cranial vault which becomes elevated and bent, gives attachment to the middle two-thirds of the falx, which is, therefore, pulled upwards by the vault. The falx is attached below to the tentorium, so that this becomes stretched, and if stress is excessive, or suddenly applied, the tentorium tears.

As has been already said, it is not the torn dura mater which is the cause of fœtal death, but the hæmorrhage, which in the majority of cases accompanies the tear, and results from the same stress.

Source of the Hæmorrhage.—In only five cases in this series was it found that the meningeal tear had involved one or other of the sinuses. Some other site and cause of the bleeding must be sought in the majority of cases. In one, the vein of Galen was torn, but in no other case than these six could the source of bleeding be ascertained at autopsy. It was hoped that the exact location of the blood might be helpful in this determination. To this end, following the suggestion made by Holland, ten fœtal heads were injected with strong formalin, and allowed to soak in 10% formalin for 14 days. In five of these, hæmorrhage was found associated with tears of the tentorium. The hæmorrhage in one case was very extensive, but in the remaining four was localised within certain definite limits on the upper surface of the brain between the transverse fissure in front and the torn tentorium behind. The veins in this region are those of the velum interpositum and their tributaries. Each vein of Galen begins at the apex of the velum interpositum, by the union of the vena terminalis with the choroid vein. They terminate by union beneath the splenium of the corpus callosum to form the great vein of Galen, which passes backwards and slightly upwards to end in the anterior extremity of the straight sinus. In addition to the two veins of Galen from which it is formed, it receives tributaries from (1) the gyrus cinguli, (2) the pineal and quadrigeminate bodies, (3) the medial and inferior surfaces of the occipital lobes of the brain,

and (4) the upper surface of the cerebellum. In the fœtus, the veins of Galen can readily be distinguished, especially in cases of torn tentorium, where they are found to be engorged with blood; but their smaller tributaries cannot be differentiated. In one case only was there actual rupture of the vein of Galen, therefore in the majority of cases it is the smaller tributary veins which are torn. Holland believes that the commonest source of bleeding in these cases is from the small veins from the mid-brain and cerebellum that enter the vein of Galen, and also the cerebellar veins which enter the straight sinus direct. This would explain why the smaller hæmorrhages that I have seen have been localised to this area.

Mechanism of the Venous Rupture.—The mechanism which leads to rupture of these veins has been fully considered by Holland and may be briefly summarised.

Any movement of the tentorium is necessarily transmitted to the vein of Galen, whose fixed point is its entry into the straight sinus. When the tentorium is unduly stretched, the line of the vein is altered, with the result that kinking occurs at its entrance into the sinus. There is consequently enormous engorgement of the vein and its tributaries, and, if further stretching occurs, they rupture.

Intra-cranial Hæmorrhage without Meningeal Tears.—In two cases only has intra-cranial hæmorrhage been met with where there was no demonstrable tear of the meninges. In both cases, the labour was premature, and the child born alive; in each the intra-cranial findings at autopsy were identical. The left lateral ventricle was filled with blood, and the clot extended through the foramen of Monro into the third ventricle, and from there, through the aqueduct of Sylvius, into the fourth ventricle. Much blood was found beneath the cerebellum and surrounding the medulla, extending along the cervical canal.

The actual source of the bleeding in these cases is a controversial point. Most writers seem to assume that it comes from the choroid plexus, but its profuseness seems rather to point to the rupture of larger veins than those of the plexus.

In these two cases hæmorrhages in other parts of the body were associated with the cranial lesion. They are of interest in regard to the 'Hæmorrhagic Diathesis of the New-Born,' which will be discussed later in the consideration of the general ætiology of hæmorrhages of the new-born.

(iii) *Gross Visceral Hæmorrhages.*

Supra-Renal Hæmorrhage.—Eight cases of hæmorrhage into one or both supra-renal glands have been found; all but three of these were associated with intra-cranial hæmorrhage. Spencer in his monumental work records

hæmorrhage into the supra-renals as occurring 26 times, but in some of these cases the hæmorrhage was small in amount, or it is noted as occurring round the organ and not actually into it. Extensive hæmorrhage with rupture of the capsule occurred in three cases of his series, and he gives notes of delivery in two. Both were large fœtuses delivered by the breech, the second after version and through a contracted pelvis. He points out that 'delivery by the lower pole (especially when traction is employed) greatly favours the production of this injury.'

It is interesting to compare Spencer's results with those of more recent work, when it is found that they are strikingly similar. The 34 years of obstetrical technique cannot have influenced to any marked degree the factors which are responsible for the production of these lesions.

TABLE VI.

Analysis of Eight Cases of Supra-Renal Hæmorrhage.

No.	Age of fœtus.	Right or left supra-renal.	Associated hæmorrhages or tears.	Mode of Delivery.	Notes.
2	F.T.	L. & R.	Torn Tentorium	Breech	Mother toxæmic
5	F.T.	L. & R.	—	Breech	Lived 3 days
10	8 m.	L. & R.	Torn Tentorium	Breech	—
21	F.T.	L. & R.	Torn Tentorium	Transverse lie, version, breech delivery	—
33	8 m.	R.	Torn Tentorium Ruptured Liver	Placenta prævia, version, breech delivery	—
37	7 m.	R.	—	Vertex presentation; no forceps	Lived 4 days
100	F.T.	L. & R.	Ruptured Liver	Placenta prævia, version, breech delivery	—
126	F.T.	L. & R.	Torn Tentorium	Transverse lie, version, breech delivery	—

It will be seen that the truth of this observation of Spencer's has been fully proved in the present investigation, for, out of the eight cases, seven or 87·5% occurred in breech deliveries. Of these seven, three were in

primary breech deliveries, and four in breech after version. The indication for version is given in Table VI.

Hæmorrhages of the Liver.—Five times have hæmorrhages of large size been met with in the liver, and in four of these the liver has been ruptured, giving rise to excessive intra-peritoneal hæmorrhage. A short analysis of the five cases is given:—

TABLE VII.

Analysis of Five Cases Showing Hæmorrhage in Liver.

No.	Capsule of Liver.	Associated Hæmorrhages and tears.	Method of Delivery.
33	Unruptured	R. Supra-renal Tentorium torn	Placenta prævia, version, breech delivery
34	Ruptured	Tentorium torn	Transverse lie, version, breech delivery
100	Ruptured	R. & L. Supra-renal	Placenta prævia, version, breech delivery
113	Ruptured	Tentorium torn	Transverse lie, version, breech delivery
117	Ruptured	None	Placenta prævia, version, breech delivery

It is very noticeable that in every case where the liver was ruptured, version had been performed. The association of other hæmorrhages in all but one case is also of note. The one case (No. 117) where the only hæmorrhage found had occurred in the liver is of interest. The mother was admitted with accidental hæmorrhage and version was performed. Natural delivery of a breech followed, but the cord was found to be tightly stretched between the legs. The fœtus was still-born, well-developed and obviously at full term. At autopsy the peritoneal cavity contained much blood, and it was found that the bleeding was coming from the under surface of the liver. Here the capsule was ruptured. The tear had occurred at the insertion of the round ligament, and was a slit about ¾ in. long, parallel with the hepatic fissure. This appearance suggested the possibility that in this instance, at any rate, the rupture of the liver might have been caused by undue traction on the cord.

Other Visceral Hæmorrhages.—Large hæmorrhages have also been seen into pleural cavities, extensively into the lung substance, into the perirenal

tissue, and into the kidney itself. In two cases hæmorrhages into many organs were met with.

ÆTIOLOGY OF HÆMORRHAGES OF THE NEW-BORN.

Such a record of fatal bleeding occurring during delivery or soon afterwards is of obvious significance, and it is not to be wondered at that during the past few years an extensive literature dealing with its causation has accumulated. Two predisposing ætiological factors and three immediate causes of hæmorrhage emerge from a mass of speculation.

Predisposing Factors.—These consist of (a) Prematurity, and (b) Syphilis, and of them little need be said. What has been stated of the tissues generally applies particularly to the vessels; imperfectly formed structures are more liable to damage than those whose development is complete.

It may be suggested here that syphilis does not necessarily act in damaging the fœtal tissues, but possibly by its effect in causing prematurity.

Immediate Causes.—Here have to be considered (a) Congestion, (b) Hæmorrhagic Diathesis of the New-Born, and (c) Trauma.

(a) *Congestion.*—The influence of asphyxial congestion as a predisposing cause of hæmorrhage was first pointed out by Ashley in 1890; Cruikshank[6], however, goes further and states that congestion *per se* is the essential element. He says that 'with regard to the ætiology of hæmorrhage the factor of greatest importance appears to be the passive congestion produced by pre-natal and intra-natal asphyxia.' The degree of congestion depends chiefly on the length of time which elapses between the interruption of the exchange of gases in the placenta and the establishment of pulmonary respiration. The next most important element he believes to be the increase in congestion brought about by the passage through the birth canal; while injuries due to abnormalities of presentation or to operative interference occupy the third place in the ætiology of these lesions.

(b) *Hæmorrhagic Diathesis of the New-Born.*—Townsend in 1891 read a paper before the Boston Medical Society in which the term 'hæmorrhagic disease of the new-born' was applied to a condition in which effusions of blood occur, apparently spontaneously, in various parts of the body. He was inclined to favour the view that these were in their origin infective. He was probably the first to make a clear differentiation between such spontaneous hæmorrhages and those due to trauma.

The importance of the hæmorrhagic diathesis was not realised until Robert M. Green suggested in 1914 that birth hæmorrhages might be solely the local manifestation of a hæmorrhagic tendency. Warwick, Munro and Eustis, and many others emphasised the importance of this contention. Bodda's work on the blood-coagulation time in the new-born is of great

value in this connection. The normal coagulation time he found ranged at birth from five to nine minutes. On the second day of life the blood-coagulation time was slightly increased, and the time lengthened until it reached its maximum on the fifth day. Then a return to the average of the first day was reached by the tenth day. Evidence of hæmorrhage appeared to be a prolonged bleeding time with a delayed coagulation time. He concluded that there were factors other than trauma concerned with cerebral hæmorrhage, and that the obstetrician was carrying burdens unduly laid on him. Other observers, grouping these two factors of congestion and fœtal disease together, have come to the conclusion that the number of cases of hæmorrhage which might properly be classed as traumatic in origin is quite small.

(c) *Trauma.*—Spencer, in his pioneer work in 1891, laid stress on the mechanical traumatic factor in the ætiology of hæmorrhage, and the exact mechanism of intra-cranial trauma was definitely established by Beneke. It has been fully confirmed by many other investigators, especially by Holland, Capon and Ehrenfest.

Ætiological Factors in the Present Series.

From a consideration of this series of 160 cases, the dominance of the traumatic factor is made evident. In the great majority of cases of intra-cranial hæmorrhage, other signs of injury are manifest, such, for example, as tearing of the meninges, or in rarer cases fracture of the skull.

It is certain that venous congestion must be taken into account, but I believe as a predisposing, not as an immediate, cause of hæmorrhage. The wall of a distended vein will rupture much more easily than the wall of one less completely filled with blood, and the resulting hæmorrhage will be much greater in amount in the former case.

Anoxæmia may cause capillary oozing and petechial hæmorrhages, but trauma is responsible for those gross hæmorrhages which either kill the fœtus or cripple the child.

Trauma producing cerebral hæmorrhage is the root cause of many deaths clinically ascribed to asphyxia. The asphyxia is really due to mechanical pressure on the respiratory centre in the medulla by extravasated blood.

With regard to the 'Hæmorrhagic Disease of the New-Born,' it seemed to me, early in the work, that in certain instances, the traumatic element was insufficient of itself to cause the enormous amount of hæmorrhage found at autopsy. With Rodda's work in view, I undertook a series of investigations as to the blood-clotting time in these children and their mothers, using the apparatus consisting essentially of a small glass tube containing a lead shot. One interesting fact became obvious at once—that the blood-coagulation time of the child on the first day is that of the mother. After

the first day, the time was found to be a little prolonged until the end of the first week, returning to the normal at the end of the second week. In only four cases was there noticeable delay in the clotting time; these cases are, however, extremely interesting in that they are of the type in which a mild degree of trauma gave rise to severe hæmorrhage. Two of these cases have been described above under the heading, 'Intra-cranial hæmorrhages apart from tears of the meninges.'

The two other cases in which delay in the clotting time was noted were both full-term children, born alive. Each lived for several days, and it was possible to record the alterations in the coagulation time. At autopsy numerous large hæmorrhages were found as follows:—In one, hæmorrhage into the skin, sub-peritoneal tissue, under the capsule of the liver, and into the peri-nephric tissues. In the other, extensive hæmorrhage into both lungs, sub-capsular hæmorrhage in the liver, and hæmorrhages between the layers of the falx and tentorium.

TABLE VIII.

A Record of the Blood-Coagulation Time in Four Cases.

No.	Hæmorrhage.	Blood-clotting time.			Age at death.
		1st day.	3rd day.	7th day.	
93	Multiple	11 mins.	13 mins.	—	3 days
134	Intra-ventricular	22 mins.	—	—	36 hours
141	Multiple	9 mins.	11 mins.	13 mins.	7 days
150	Intra-ventricular	29 mins.	—	—	12 hours

For normal infants, it was found that the blood-clotting time on the first day was less than five minutes, and this time was not exceeded in the great majority of the children in which gross hæmorrhages at autopsy were found. There appears to be, however, a small group of cases in which a hæmorrhagic tendency exists. Evidently, in these instances even a mild degree of trauma may lead to severe and progressive hæmorrhage.

There must be no exaggeration of this factor. Stress should rather be laid on the importance of trauma during delivery as an ætiological factor in the causation of fœtal death. Consequently it may be hoped that the improvement of obstetrical technique will avert many of these fœtal tragedies of delivery.

Conclusions on the Ætiology of Hæmorrhages of the New-Born.

The following classification of ætiological factors is suggested:—

Predisposing Factors:

(1) Prematurity (with which *syphilis* is possibly included).

(2) Venous Congestion.

(3) Hæmorrhagic Disease of the New-Born.

Immediate Factor:

Mechanical Trauma.

II.—FŒTAL INFECTIONS.

Under this heading are included two different types of cases: one in which the cause of death is a true fœtal infection, and one in which the infective agent attacks the new-born child. In the latter class the disease does not differ much from that occurring in later infancy, and I do not propose to discuss these cases.

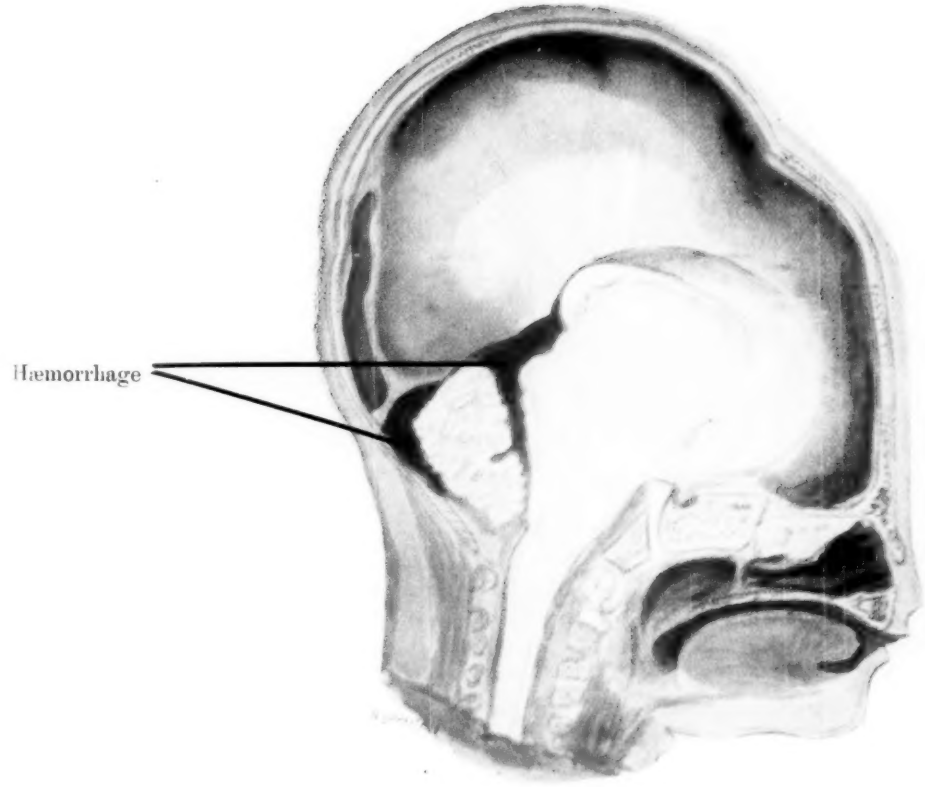
An infective process which attacks a fœtus must be modified by the intra-uterine environment. The disease may begin early in the course of fœtal development, and the fœtus, protected as it is by the amniotic fluid, and provided with an adequate blood supply, yet may be able to live. But, after birth, when the maternal blood supply is cut off and the protection is removed, the condition may prove fatal to the child. It seems possible, too, that there are infections which gain access to the fœtus during its passage through the birth canal. Of this group pneumonia forms an example.

Pneumonia.

F. Browne[4A] has said that pneumonia is the commonest cause of neo-natal death. In my experience this is true only after the exclusion of the complications of delivery, which, though they may be insufficient to cause still-birth, render the child unfitted to meet the stress and strain of neo-natal life.

I have seen nine cases of pneumonia; in seven the child was born alive and died of pneumonia before the end of the first week. In this series of 160, 43 were autopsies performed on children who had lived, so that the percentage of deaths from pneumonia is 16·3. In each case the infection has run a very rapid course, and the symptoms have been so few that only once was pneumonia suspected, the diagnosis being based on the cyanosis of the child and its rapid and wheezing respirations. The histories have, in all except one case which I believe has a different ætiology, one point of similarity, namely, prolongation of the time between the rupture of the membranes and the birth of the child.

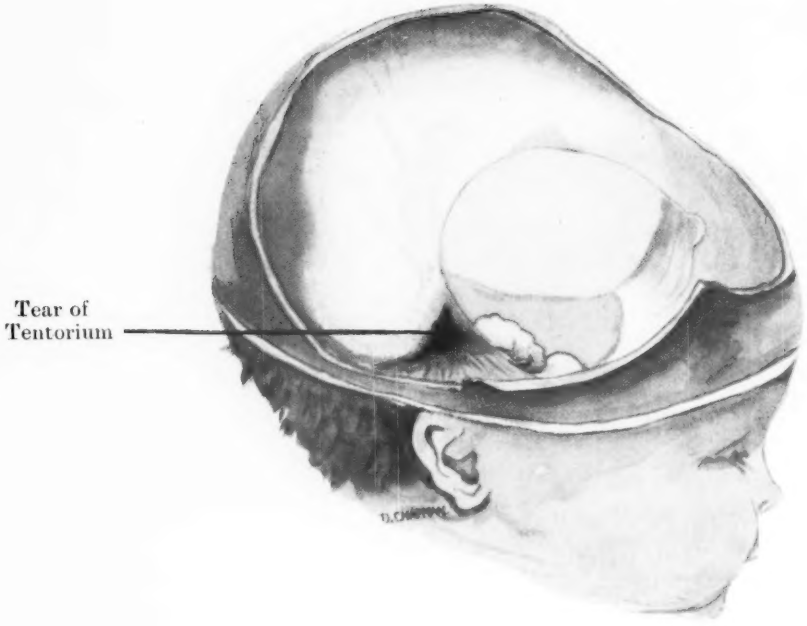
Sections of the lung tissue have been made in every instance, and in all except one, the condition has been that of broncho-pneumonia of catarrhal-celled type. The sections show a patchy consolidation, the



SAGITLAL SECTION OF FŒTAL HEAD.

Case No. 108.

Showing sub-tentorial hæmorrhage.
Note the shape of the head after moulding.



FŒTAL HEAD.

Case No. 126.

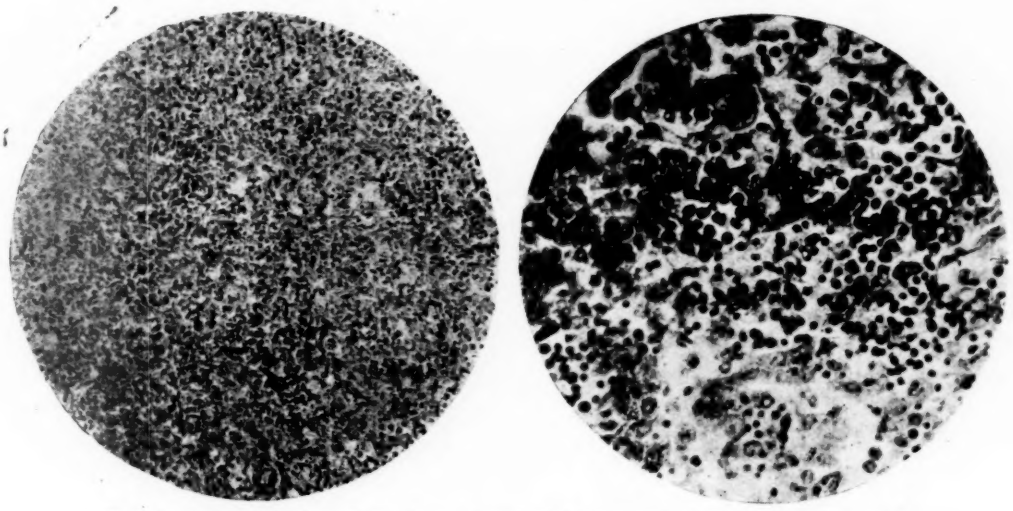
Opened after the Beneke method, showing a tear of the right side of the tentorium, and sub-tentorial hæmorrhage.

consolidated patches being confined to the areas surrounding bronchi. In these regions, the alveoli contain many large catarrhal cells, a few

Case No. 8.

Micro-photographs of section of the Lung.

Low power. High power.



Showing consolidation of the lung tissue with accumulation of catarrhal cells

polymorphonuclear leucocytes, a few red blood cells and a fluid containing fibrin. The vessels are much congested, and in most cases the areas surrounding the pneumonic patches show emphysema.

Cultures were made from the lung substance in every instance; three times a pure growth of B. Coli Communior was obtained, once a pure growth of B. Coli Communis; three times coliform bacilli were found, but the cultures were contaminated by diphtheroid and other organisms. In one, cultures from the lung grew a staphylococcus and a long chained diplo-streptococcus, and in another a pure growth of pneumococci was obtained. It has been put forward that in these cases of pneumonia, especially where the causal organism is of the coliform group, the bacillus enters the ruptured amniotic sac from the vagina of the mother and so reaches the nose and mouth of the fœtus. This being so, a delayed period between the rupture of the membranes and the birth of the child would be expected as an ætiological factor. It has been shown that in this series the only factor that could be found in common to all cases, with the one exception mentioned, was this delay in the second stage of labour. It is of interest in this connection to note that Browne in 1922 recorded a case where cultures were made from the throat of an apparently healthy infant immediately after birth in which the membranes had been ruptured 60 hours before delivery. Here cultures yielded a growth of Bacillus Coli and diphtheroid bacilli.

In some of the earlier cases of the series, it seemed to be that the pneumonic condition must have been existing, and even well advanced before birth, for, in the body of one child who lived ten hours, extensive hepatisation and fibrinous pleurisy were present. Two cases occurring later in the series, have made it possible to place the contention beyond doubt.

One of these was that of a full-term female fœtus, whose mother was admitted with a right occipito-posterior presentation. Manual rotation was effected, and the fœtus was extracted with difficulty by means of forceps. The membranes had been ruptured about 48 hours before delivery. At the autopsy on the child, extensive patches of pneumonia in the stage of grey hepatisation were found in both lungs. There was no pleurisy. Cultures from the lung surface gave a pure growth of B. Coli Communis.

The other was also a full-term female fœtus delivered by craniotomy after unsuccessful applications of forceps. Here delivery was effected more than 60 hours after the rupture of the membranes. The lungs of the fœtus showed a patchy consolidation with broncho-pneumonia of catarrhal-celled type. Cultures from the lung yielded a pure growth of B. Coli Communis.

It is evident from these cases and from similar cases recorded, that broncho-pneumonia may be present and even well advanced before birth.

A further case already mentioned is of considerable interest from the point of view of the possibility of the transference of disease from the mother to the fœtus. It has been said already that this case cannot be brought into line with the other cases of pneumonia, either with regard to its ætiology or to its bacteriology.

A full-term female child was delivered by Cæsarian section, the membranes being unruptured before the operation, which was performed on March 24th, 1924. The child was born alive, but had a cyanotic appearance from birth and never attained a healthy colour. Its breathing was shallow and more rapid than normal, and it died on April 1st, 1924. The mother died on the 26th March, 1924, and autopsies were performed on both. The mother had an acute bronchitis with thick purulent exudate into the bronchi, and areas of broncho-pneumonia in both lungs. Sections from the lung showed areas of consolidation surrounding the bronchioles, with much polymorphonuclear emigration into the alveoli where also a few red blood cells and entangled threads of fibrin were found. The vessels in the vicinity showed a moderate degree of acute congestion. The bronchi were seen in sections to be the subject of an acute purulent inflammation, the changes being more marked in the smaller branches of the bronchial tree.

Autopsy on the child revealed a similar condition of pneumonia. The whole of the base of each lung was consolidated and in the stage of grey hepatisation. Sections confirmed the diagnosis of pneumonia, which was certainly broncho-pneumonia by its distribution, but, unlike the other cases of neo-natal pneumonia, was not catarrhal-celled in type. The predominating cell, instead of the catarrhal cell of the other pneumonias in the series, was the polymorphonuclear leucocyte, which was present in great numbers in the affected alveoli and in the bronchioles in the centre of the consolidated areas. The vessels showed much congestion and polymorphonuclear leucocytic migration into the surroundings. Instead of the coliform bacilli, which were the predominating organisms in the other cases, cultures from the lung yielded a pure growth of pneumococci.

It seems feasible that in this case infection was conveyed from the mother to the fœtus, either by means of the placental circulation or indirectly. Direct transmission to the child is unlikely, as, though the child lived seven days, the mother lived for

two days only after delivery, and during this time there was no direct communication. It must be remembered, too, that from its birth, the child showed symptoms of pulmonary embarrassment.

One case of pneumonia is of interest from a medico-legal aspect. The child was three days old and appeared quite healthy till two hours before its death, which was dramatically sudden, and might, in other circumstances, have given rise to the suspicion of foul play, or of overlying. At the autopsy, small areas of broncho-pneumonia were found. The outstanding feature, both macroscopically and microscopically, was the amount of hæmorrhage which had occurred into the lung substance. Cultures from the lung were sterile. It has been said that the ætiological feature in such cases as this is usually organismal, but Browne states that 'there is evidence to support the theory that it may occasionally be of the nature of an anaphylaxis.'

III.—FŒTAL ANOMALIES.

This heading includes the cases of mal-development, and the morbid states which cannot, at present, be assigned to any known infective agent.

A list of those exemplified in the series has been given, and some are singled out for further reference.

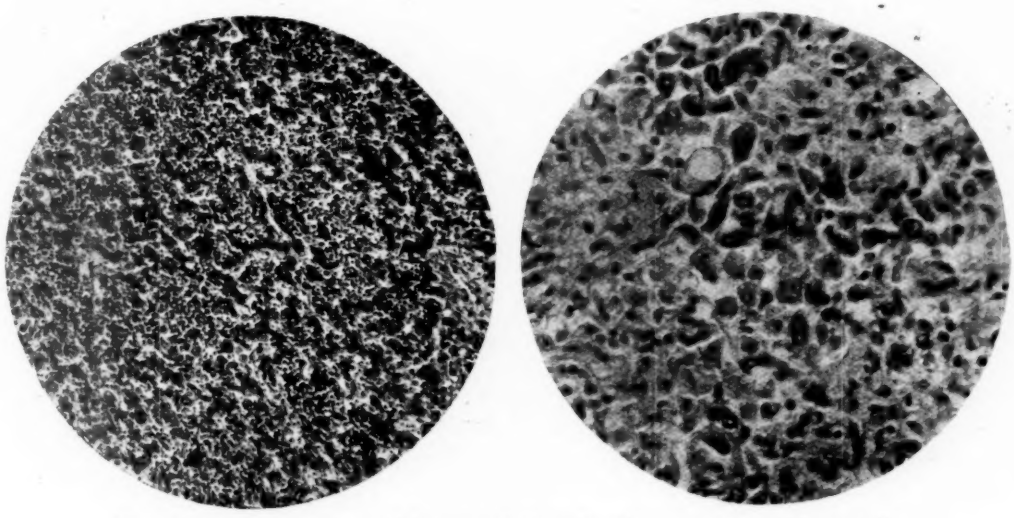
General Œdema of the Fœtus.

This is a rare condition of which I have seen one case. Ballantyne[1] [2] defines the condition as 'a rare condition of the fœtus, characterised by general

Case No. 136.

Micro-photographs of sections of the Liver.

Low power. High power.



Showing the aggregation of hæmo-poietic cells, the separation of liver cells, and their pigmentation.

anasarca, by the presence of fluid effusions in the peritoneal, pleural and pericardial sacs, and usually by œdema of the placenta; and resulting in the death of the fœtus or infant before, during, or very soon after birth.'

It will be seen that the case to be described fulfils the conditions necessary to be placed in this category.

CASE.—The mother was 36 years old, tall and well built. She had had six previous children, all being normal deliveries of full-term healthy infants born alive, and during the pregnancies she had been well. The œdematous fœtus was born at 7½ months. During the last month of the pregnancy the mother noticed coloured spots before her eyes at intervals, and she also had vague abdominal pains. Six days before delivery her feet and ankles became so swollen that she could not get her shoes on. Before delivery there was extensive hæmorrhage, the estimated loss being about one pint.

A catheter specimen of urine was obtained on the day of delivery. The specific gravity was found to be 1010 and the reaction acid. A heavy cloud of albumen was present, but chemical tests for other abnormal constituents were negative. On microscopical examination of the centrifuged deposit, a few pus cells were seen but no red blood cells and no casts or crystals. Stained films showed an absence of organisms.

Clinically, the mother showed a severe anæmia due to the blood loss, but no other lesion was demonstrable.

Under general anæsthesia, the membranes were ruptured and a leg brought down, and later a still-born fœtus was delivered by the breech.

The fœtus was a male, obviously premature, its age corresponding apparently with the estimated 7½ months gestation. The weight was 1680 gms. and the length 15½ ins. The abdomen was protuberant, and there was generalised œdema, especially of the face, chest, abdomen and external genitals. There was a clean cut wound of the skin and subcutaneous tissues along the fold of the left groin due presumably to forcible extension of the thigh during delivery. Clear yellow fluid flowed from any incision made into the subcutaneous tissues.

Post mortem examination showed small hæmorrhages between the scalp and the skull. There were no meningeal tears, but small hæmorrhages were present between the two layers of the falx cerebri and between the two layers of the tentorium cerebelli. No intra-cerebral hæmorrhage was found. The brain was œdematous and the ventricles were slightly distended with clear yellow fluid. The pleural cavities each contained about 10 ccs. of similar clear yellow fluid; the lungs had not been ærated but were apparently normal, the thymus was not enlarged, but was softer and more friable than usual; the thyroid and lymph glands were not enlarged. The pericardial sac contained about 10 ccs. of clear yellow fluid; the heart showed no congenital or other abnormalities. The peritoneal cavity contained about 200 ccs. of clear yellow fluid, and there was a little fibrinous deposit on the surface of the viscera in places, and on the peritoneal aspect of the abdominal wall. The liver was normal in appearance and consistency, and weighed 150 gms.; the umbilical vein and ductus venosus were patent and the gall bladder was distended with bile. The spleen weighed 40 gms., was deep red in colour and firm in consistency; pancreas, mesentery, stomach and intestines appeared healthy. The supra-renals showed many sub-capsular hæmorrhages, but otherwise appeared normal. Each kidney weighed 22 gms. and both appeared normal; there was no evidence of fœtal nephritis, macroscopical or microscopical. The ureters and urethra were proved to be patent, and the bladder contained a little straw-coloured urine. There was much œdema of the scrotum. The left testis was still in the abdominal cavity at the level of the brim of the pelvis, the right testis being in the scrotum.

The placenta weighed 1210 gms., was bulky and very friable, dense white in colour. Much blood clot was present on the maternal side. The umbilical cord was 19 inches in length, ½ inch in diameter, and Wharton's jelly appeared very translucent. A drop of fœtal urine was examined for albumen, and a faint cloud was found to be present.

The ætiological factors of general œdema on which stress has been laid in the literature may be classified as (i) maternal, (ii) paternal and (iii) fœtal.

(i) Four maternal causes have been suggested.

(*a*) Ballantyne laid emphasis on the advanced age of the mother in these cases of fœtal œdema. This was in 1902, and in Schumann's[14] list compiled in 1915, only 13·3% of cases occurred in mothers over 35 years of age. (In the present case the mother was 36.)

(*b*) In the great majority of the recorded cases there is some evidence of toxæmia in the mother, and this usually takes the form of albuminuria, œdema or excessive vomiting.

In the case under consideration now, the urine of the mother, on admission, contained a dense cloud of albumen; no blood, and casts were not found. There was marked œdema of the lower extremities and abdominal wall. She complained of ' coloured spots ' before her eyes; there was no history of excessive vomiting, of headache, or of fits. She was admitted to hospital with accidental hæmorrhage.

(*c*) Spirochætes have once been found in the tissues of an œdematous fœtus, and in a few instances the maternal blood has given a positive Wassermann reaction, but in the great majority of cases, there has been no evidence of syphilis either clinically in the mother or found at autopsy in the child. In our case there was no evidence of syphilis, and the maternal Wassermann reaction was negative.

(*d*) Ballantyne first drew attention to the fact that the mother of an œdematous fœtus is often anæmic. The mother, in our case, was very pale owing to loss of blood, but there was no previous history of anæmia.

In weighing the importance of maternal morbid states as a causative factor, it must be remembered that while such maternal conditions are, unfortunately, all too common, fœtal œdema is, as Ballantyne states, a rare condition. It is reasonable to assume that there is some other factor as yet unknown. This may be directly causative or acting by means of the maternal condition.

(ii) Some writers have suggested various paternal disorders as a possible causation, *e.g.*, œdema in the father, lead poisoning, etc. The father in our case was not examined except during the taking of blood for a Wassermann reaction, no gross lesions were obvious; his size and physique were normal; there was no history of working in lead and his Wassermann reaction was negative. It seems that little reliable evidence is forthcoming on the importance of such paternal disease in fœtal morbidity.

(iii) In certain cases described, actual mechanical obstruction to the vascular or lymphatic system of the fœtus has been found. Such structural defects as, for example, complete absence of the lymphatic system as recorded by Smith and Birmingham[17] in 1899, might be reasonably brought

forward as the cause of generalised œdema, but in some cases it is difficult to ascertain the actual way in which the lesion produced the œdematous state. It has been said that in all cases, a mechanical cause can be found if a thorough post mortem examination is made, but this contention has not been supported by later experience. In a certain number of cases, congenital abnormalities have been found associated with the generalised œdema, but congenital abnormalities occur by no means infrequently in any series of still-births (*e.g.*, 9% of the present 160 cases), and it is possible that the associated conditions may be due to one and the same cause.

I examined the œdematous fœtus as carefully as was possible with a view to discovering any manifest mechanical cause for the œdema, but I was unable to demonstrate any obstructive lesion, either cardiac as recorded, *e.g.*, by Tait[19] in 1895, or umbilical (*see* Crozier and Fischer).

The case under consideration, then, comes under the heading of non-obstructive causation, and many other examples are to be found in the writings.

Schridde[15] in 1910 first drew attention to certain histological features, and the cases reported since have shown similar pathological findings.

It would, at this stage, be as well to describe the histological appearances as I saw them. The most active changes were found in the liver. Here normoblasts, megaloblasts and myeloid cells were seen in enormous aggregations so that groups of liver cells were cut off from one another by the hæmopoietic cells. The latter were showing well-marked karyokinetic figures. This accumulation of cells did not affect any particular part of the liver tissue more than another nor was there any demonstrable increase in the connective tissue of the liver. This does not agree with some of the described cases where it is stated that the periportal connective tissue is increased in quantity and that the hæmopoietic cells tend to accumulate in the region of the vessels within this periportal tissue. The liver cells themselves contained a golden brown pigment which, by means of potassium ferrocyanide and hydrochloric acid was shown to contain iron. In the spleen, a similar change was found, but not so advanced in degree. An accumulation of myeloblasts, megaloblasts and normoblasts had to a certain extent replaced the normal spleen tissue. Again karyokinetic figures were evident, and in the lymphoid cells of the spleen a small amount of an iron-containing pigment was found. The kidneys showed a similar accumulation of cells, but in much less degree than in liver and spleen. There was no evidence of fœtal nephritis, and no pigment was demonstrated. Search for the spirochæta pallida proved futile.

In assessing the value of this evidence, I have borne in mind the fact that we were dealing with a premature fœtus, and that during later fœtal life, the liver and spleen, along with the bone marrow, are the sources of the solid elements of the blood. To this end, we have sectioned the livers of premature children, normal, and abnormal of approximately the same age as the œdematous fœtus. Here we have found small clusters of nucleated red blood cells, normoblasts with a few megaloblasts always placed in definite situations between the columns of liver cells. The livers of syphilitic infants are said to contain many of these cell clusters; this is assumed to be a response to the destruction of red cells brought about by

the circulating toxin. In the liver of an œdematous fœtus, however, it is such a gross exaggeration of these processes as to show a grade of hæmopoietic response not met with in other conditions. The fact, too, that a similar response is met with, not only in the liver, but also in the spleen, and probably, though to a less extent, in the kidney, seems to show that all possible sources of blood formation are being tapped. The presence of an iron-containing pigment in the cells of the liver and spleen, points to a co-existing destruction of red blood cells.

The view appears justified that some unknown toxin is being elaborated, destroying the red blood cells and calling into being all the potential sources of blood-cell formation.

The question of the origin of the toxin of fœtal, placental, and maternal elaboration, cannot in our present state of knowledge be decided.

Congenital Abnormalities of the Heart.

Four cases of congenital heart lesions occur in the series, and I am including a fifth example which I obtained at the Royal Hospital, Sheffield, from a child who died there at the age of five weeks.

Three of the five are of the type described as pulmonary stenosis. The hearts showed gross enlargement especially of the right side. The pulmonary artery was in each case small in calibre and there was varying degree of stenosis at the pulmonary orifice, though there was no evidence of fusion of the cusps. In no case was the stenosis complete, but the fifth case is of interest because the child lived for five weeks and yet the stenosis was so extreme that it is questionable if more than minute quantities of blood had been received by the lungs through the contracted orifice.

These three cases show the effects of arrest of developmental expansion of the infundibular cavity first described by Keith. There is frequently an associated defect in the interventricular septum, and this was found in two out of the three cases here described, but the foramen ovale and ductus arteriosus did not differ in any particular from those of a normal full-term still-born fœtus, and the auriculo-ventricular valves and the aorta with its valves showed no lesions.

In these cases of severe pulmonary stenosis, it is difficult to understand how the pulmonary circulation is carried on especially after birth. This difficulty suggested itself to Keith, who injected the arteries in one of these cases and found that the bronchial arteries and other accessory branches derived from the intercostals were enormously enlarged in size and increased in number, and it is to be presumed that the arterial system of the lungs is filled from the systemic-circulation.

No. 4 of the series of congenital heart lesions showed a less common condition, namely, almost complete atrophy of the body of the right ventricle, with absence of the tricuspid valve. There was a large central

interventricular foramen. The foramen ovale and ductus arteriosus were patent, the fœtus being still-born. It is from cases similar to this that Keith illustrates what he calls ' the dual constitution of the right ventricle,' for here there is no stenosis of the pulmonary valve and the infundibular part is expanded, while there has been arrest of the development of the body of the right ventricle.

No. 5 of this series showed the opposite condition, namely, considerable atrophy of the left ventricle. Here, the right side of the heart appeared a little larger than usual, but the left ventricle was so small that the cavity did not admit the tip of the little finger. The mitral valve was not demonstrable, this corresponding with the absence of the tricuspid valve in No. 4. In these cases the obliteration of the valve is probably due to the fusion of the endocardial tissue out of which the valve cushions are fashioned. Here the aorta was very narrow and the ductus arteriosus was not abnormally patent and yet the child lived three days. The foramen ovale was patent, and there was a small central interventricular foramen. This case was of interest, too, because small recent and friable vegetations were found on the tricuspid and pulmonary valves, there being no evidence of stenosis of these valves. Microscope sections showed the presence of masses of fibrin with entangled red blood cells and leucocytes. No bacteria could be found.

In this instance it is obvious that the endocarditis evinced at autopsy was not the cause of the gross heart lesions found. It is possible that the same process operating in very early fœtal life and causing arrested development had, acting in the later months of intra-uterine life, given rise to a definite acute endocarditis, but it must be remembered that a damaged structure is more prone to bacterial damage than one normal and healthy.

It will be seen that in every instance but one there was defect in the interventricular septum. This is very commonly found in association with other malformations especially with pulmonary stenosis and occasionally is met with alone. It was suggested by Meckel that the interventricular foramen might be the primary lesion, the pulmonary stenosis occurring subsequently. The exact sequence of events which lead to the closure of the interventricular septum is not known, but from the fact that the foramen disappears as soon as the infundibulum becomes incorporated with the right ventricle, it would seem that the expansion of the cavity of the bulbus cordis must play an important part in its closure. Thus the work of Keith points to the view that the failure to close of the interventricular foramen is a condition secondary to other developmental errors.

The association of cardiac anomalies with other instances of faulty development is a well-established fact, for example, Vierordt found that associated defects occurred 80 times in 700 cases, while Abbott found it in

20% of cases. Of the five cases recorded here, two also showed absence of the right kidney and ureter, and one of these two was, in addition, hydrocephalic.

Garrod has pointed out the association of Mongolian deficiency and congenital cardiac lesions. In two of our five cases there were definite signs of Mongolism. That is to say that in one case only was there no other defect found in association with the mal-development of the heart.

ACHONDROPLASIA.

In this series is one case of Achondroplasia.

The family history was enquired into with care, but no evidence of antecedent dwarfism was obtained. The mother was intelligent and of good education. She was 32 years of age when the achondroplasiac child was born. This was her second child, the first having been born four years before and being alive and apparently normal in all respects. The achondroplasiac child was born at full term, a normal breech delivery. The only abnormality found in the mother was an asymmetrical pelvis due to a fracture of the neck of the femur which had caused much shortening. Her Wassermann reaction was negative.

In this case at first glance it seemed apparent that the child's head was too large, while its limbs were too short. On measurement, however, it was found that only part of these assumptions could be substantiated. The size of the head was not increased; the circumference being that of a normal child of the same development. The limbs were found to be very short. When vertical, the arms reached only to a point midway between the crest of the ilium and the great trochanter. The lower limbs were only about half the length of those of a normal child. The chief diminution in length, as in all cases of achondroplasia, was in the humerus and femur respectively. Taking the length of the humerus in the normal infant as 6 cms. both were excessively shortened, the right humerus measured 3·2 cms. and the left 3·3 cms., the radius and ulna were of equal length, each measuring 2·9 cs. The femora were of equal length each measuring 6 cms., and there was on each side a slight concavity inwards of the shaft. The fibulæ measured 4·4 cms. each, and the contour was normal. The hands showed to a moderate degree that anomaly first pointed out by J. Thomson. The palm is flat, and the fingers, instead of being parallel, diverge, two to the ulnar and two to the radial side, forming the so-called 'trident' hand. The ribs were very short (the maximal length being three-quarters of an inch) while the costal cartilages were long. A deep depression was seen at the junction of the ribs with the costal cartilages. The trunk was of normal size and shape.

Morbid Anatomy.—Microscopic sections were made through the lower end of the right femur, but nothing was seen except an alteration in the normal parallel arrangement of the cartilage cells and a comparative dearth of vessels. In some cases described the epiphysis has been separated from the diaphysis by an ingrowth of connective tissue derived from the periosteum.

The internal organs showed no pathological change, and no other congenital abnormalities found, though these were sought, remembering that such had been recorded. For example, Nathan[12] described congenital hernia in association with achondroplasia, and Kassowitz congenital dislocation of the hip.

The thyroid was sectioned in view of the case described by Symington & Thomson, but no lesion found. The pituitary gland, macroscopically appearing normal was, unfortunately, not examined microscopically.

CONGENITAL GOITRE.

One case of congenital enlargement of the thyroid has been met with.

This was in a still-born 7½ months fœtus, that presented by the breech. The mother had no swelling of the thyroid, and had had two children previously born alive and normal in all respects. In this fœtus there were many associated abnormalities. Spina bifida was present in the lumbo-sacral region with meningocele, and there was a large umbilical hernia which contained not only many coils of small intestine, but also the gall bladder and a tongue of liver substance derived from the right lobe.

The thyroid itself formed a large mass in the front of the neck occupying the whole region between the chin and the manubrium sterni, the tissues being œdematous over it. The gland, when dissected free, was found to be 3½ inches long, about 2 inches across, and, in places, over 1 inch in thickness. The whole of the gland was affected and it surrounded the trachea almost entirely.

Sections showed increase in the number of acini, and hypertrophy of the lining cells. No attempt to form colloid had yet been made.

CONCLUSIONS.

In this study of the causation of fœtal and neo-natal death in a series of 160 cases the following conclusions are reached:—

(1) More fœtuses die as the result of excessive trauma during delivery than from maternal or fœtal disease.

(2) The fatal results of excessive trauma are due to hæmorrhage.

(3) Certain maternal morbid states predispose to fœtal injury during delivery.

(4) Factors predisposing to hæmorrhage are prematurity, excessive venous congestion, and the ' hæmorrhagic diathesis.'

(5) Pneumonia is the commonest infection causing neo-natal death.

(6) The term ' congenital heart disease ' is frequently a misnomer.

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CONGENITAL ATRESIA OF THE ALIMENTARY TRACT.

BY

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In an analysis of the autopsies performed at the Hospital for Sick Children since the beginning of this century, numbering 6,000 in all, congenital atresia of some or other part of the alimentary tract has been found on 28 occasions, and it is on these cases that this report is based. In addition, congenital narrowing without complete obliteration of the lumen has been found in six cases, and a brief account of these is also given. Various other congenital abnormalities closely connected with the development of the intestinal tract, such as obliteration of the common bile duct, abnormalities associated with Meckel's diverticulum, imperforate anus, and unusual formations of the peritoneum, have not been included, being outside the scope of this paper.

The following list shows the number of cases at the various sites of obstruction:—

	Atresia.	Partial Stenosis.
Œsophagus	6	2
Duodenum { above Bile Papilla ...	2	1
Duodenum { at Bile Papilla	2	1
Duodenum { below Bile Papilla ...	2	—
Small Intestine	13	—
Large Intestine	3	2
	28	6

ŒSOPHAGUS.

The average length of life of the six cases of œsophageal atresia was nine days, the extremes being six and thirteen days.

The typical symptoms of this condition were shown in each case, and consisted of returning a mixture of food and mucus immediately after swallowing. The vomit was in every case returned through the nose as well as the mouth, and was in some cases preceded by a violent fit of coughing, during which the child became cyanosed and seemed in immediate danger of succumbing. Attempts to pass a soft rubber catheter into the stomach were inevitably unsuccessful, obstruction being met with after the tube had been passed four or five inches beyond the lips. Examination of the chest revealed in most cases evidence of bronchitis, and in four cases the temperature was raised until death, reaching in one case 106°.

In one case bile pigments were found in the vomited material, this being clear evidence of a communication between trachea and the lower end of the œsophagus below the atresia. The filling of the stomach with air during respiration or coughing, which is a further sign of such a communication, was not noted in any of the cases.

The post mortem findings were closely similar in five cases; the œsophagus ended blindly, approximately at the level of the bifurcation of the trachea, the proximal portion being considerably dilated. The distal portion of the œsophagus was narrow, and its upper end opened into the posterior wall of the trachea. In one case in which exact measurements were taken, the aperture in the wall of the trachea was $\frac{3}{4}$ inch above the level of the atresia; the upper part of the œsophagus measured $1\frac{1}{2}$ inches, the lower part 2 inches. In the sixth case the notes simply state that a complete atresia existed 3 inches from the mouth; the whole region was then removed en bloc for further dissection. Whether or not a communication with the trachea existed is not stated.

In only one case was there any further abnormality; this consisted of complete absence of the left kidney.

A considerable number of cases of congenital œsophageal atresia has been recorded. Von Reuss[1] states that more than a hundred are on record, and Cautley[2] collected and published a list in 1917. A full bibliography of the subject is given by Heumann[3], who quoting Kreuter and Vieillard, gives the percentage of cases with a communication between the trachea and lower portion of the œsophagus as between 87 and 92.

Keith and Spicer[4] described three cases, and added a developmental explanation of the abnormality. Normally the posterior rim of the opening from the primitive œsophagus formed by the evagination of the lung bud, grows forward and thus separates the œsophagus from the trachea, becoming the tracheo-œsophageal septum. Were this septum to grow irregularly, leaving a gap in its growth, a communication between the trachea and œsophagus would result. Moreover, if the part of such a septum anterior to the gap were to commence growing obliquely forwards and ventralwards from the dorsal wall of the œsophagus, the œsophagus would become divided into two portions.

The three figures demonstrate these points. Figure 1 shows the normal formation of the tracheo-œsophageal septum. Figure 2 shows the formation of a gap in the septum. Figure 3 shows the abnormal origin of the cephalic portion of the divided septum.

The treatment of this condition is practically hopeless. Gastrostomy was performed on two of the six cases, and other cases in the literature have undergone this operation without success. Since there is in the vast majority of instances a tracheo-œsophageal communication, if food in the stomach is vomited, it will immediately be precipitated into the trachea, and aspiration

Fig I

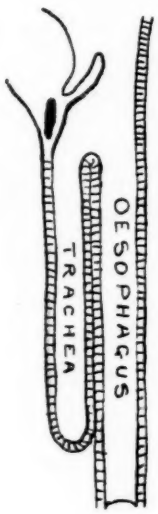


Fig II

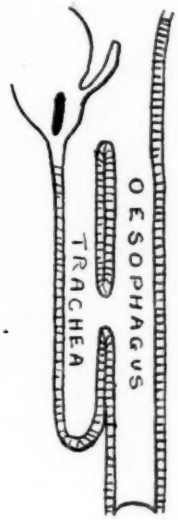
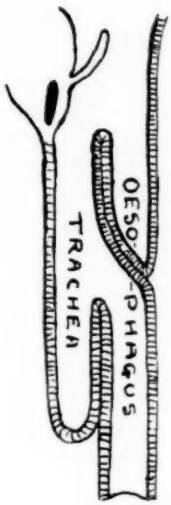


Fig III



pneumonia will result. Richter[5] has attempted to overcome this in two cases, by crushing and ligaturing the tracheo-œsophageal communication, and then performing gastrostomy. Both cases proved fatal.

Presumptuous as it must seem for one unskilled in surgery to offer a suggestion in the treatment of these cases, my excuse lies in a consideration of the mortality of the condition. It should be possible to open the stomach and pass a soft catheter through the cardiac orifice, through the tracheo-œsophageal communication into the trachea, and ultimately out through the mouth. A fan-shaped lower end to the tube should prevent its slipping back out of the stomach into the œsophagus, and at the same time prevent the vomiting of food alongside the tube. If the nutrition of the infant could be maintained and improved by this means, later operations to correct the mal-development might be more hopefully undertaken.

In the two cases of partial stenosis of the œsophagus, death occurred at the age of 3 and 4 years. Vomiting almost immediately after swallowing food had occurred on and off since birth, in bouts lasting about a week with an interval of about a month. During attacks, constipation was severe. Post mortem examination showed a fibrous stenosis in the lower third of the œsophagus, through which probes could be easily passed. These cases showed no communication between the trachea and œsophagus.

Duodenum.

No case was found of congenital atresia at the pylorus. At this position atresia is rare, only four cases having been reported. The duodenum is, however, not so uncommon a situation, the position of the atresia being

classified according to its relation to the bile papilla. In the two cases stated in the above list to be below the papilla, the actual site of the atresia was at the duodeno-jejunal junction.

The average length of life in the six cases was 12 days, the limits being 4 and 21 days. But the length of life gave no indication to the position of obstruction, for the cases living for 21 days showed atresia at or above the entrance of the bile-duct.

The symptoms of forcible vomiting dating from the first taking of food, visible peristalsis passing from left to right across the epigastrium, small motions consisting only of meconium, and progressive wasting, were recorded in most of the cases. In addition, in both cases in which the atresia was below the entrance of the common bile-duct, bile was found in the vomited material. In one case with atresia at the level of the bile papilla, the vomit was also noted to be dark brown, and at autopsy bile was present in the duodenum both above and below the obstruction. The explanation of this is that the bile-duct probably had two openings into the duodenum on each side of the atresia. The vomit contained no bile in the two examples of atresia above the bile papilla.

In both cases where the atresia was below the bile papilla, the infant was jaundiced, but the post mortem findings in these cases suggested that jaundice need not necessarily be present. Those cases which lived beyond the first week showed a remarkable degree of dilatation of the stomach and proximal portion of the duodenum, the pyloric ring being also so dilated as to render it somewhat difficult to identify. These cases would probably vomit all the bile that reached the duodenum, and so diminish the liability to jaundice.

The precise nature of the obstruction found post mortem varied. In most instances, the atresia appeared to consist of a short fibrous ring, but in one case the two portions of duodenum were completely separated, the blind end of the peripheral portion lying buried in the head of the pancreas. In another case a complete obstruction was produced by the fusion at one point of the mucosa, the other coats of the duodenum being unaffected. In one case, in addition to the atresia, complete transposition of the viscera was found, associated with absence of the spleen, or of any accessary spleen tissue.

There were two examples of incomplete stenosis of the duodenum at the level of the entrance of the common bile-duct. In one, the child lived for three weeks and at autopsy a thin trickle of water could be passed through the stenosis. The other child lived to the age of 21 months. At the post mortem, a fine probe could be passed with difficulty through the constriction.

Small and Large Intestine.

These are taken together, because in two cases atresia was found in both sections of the intestine.

Although one case reached the age of nineteen days, the average length of life was six days. Two died almost at once after admission to hospital. The remainder survived long enough for surgical treatment to be essayed, but except in one case of atresia of the rectum, death followed laparotomy within 36 hours.

The symptoms in these cases consisted of vomiting commencing with the first taking of food, absolute constipation except for the passage of a small amount of meconium, and distension of the abdomen. Usually visible intestinal peristalsis was noted, the intestines standing out across the abdomen in the typical step-ladder pattern. Vomiting did not occur in two cases; in one of these the atresia occurred in the sigmoid colon, in the other the intestine was patent as far as the middle of the rectum, where it terminated blindly.

The findings at autopsy varied. In eight cases, a portion of the small intestine was represented by a fibrous cord, which varied in length from a quarter of an inch to several feet. In one of these, the upper half of the small intestine was completely impervious, whilst below this level as far as the rectum, the intestine was uniformly small, with a minute lumen.

In six cases distinct gaps occurred in the continuity of the bowel. In one of these, no less than three gaps were found. In another a gap was followed three inches lower by a fibrous atresia. The intervening portion of small intestine had formed a volvulus. In a third, the blind end of the distal length of small intestine was adherent to a mesenteric cyst as large as a hen's egg.

In one instance, there was complete transposition of the viscera.

Finally, two examples of partial stenosis were found, both affecting the lower third of the small intestine and the whole of the colon. In these the bowel in the stenosed portion was about as large in circumference as a lead pencil; the lumen was very narrow, and filled with a white detritus. Neither of these infants lived beyond the first week of life.

Various theories have been advanced to explain these conditions, but no theory will fit all the cases. It has been supposed that fœtal peritonitis might be a cause, but further evidence of previous peritonitis is not usually to be found. Another view is that at the various points of embryological importance in the intestinal tract, errors in development have occurred. Such points would be the origin of the hepatic and pancreatic buds, or near the vitello intestinal duct, but some of the cases involve a greater length of bowel than this theory could explain, while in others, the atresia does not seem to have occurred at points of particular embryological interest. Thus in one infant the small intestine terminated 18 inches from the pylorus; in another three feet from the duodeno-jejunal junction.

It has been shown that in the duodenum, and probably throughout the intestines, there takes place during development an epithelial proliferation

sufficient to block the original lumen. This proliferation is later removed, but should the condition persist in places, atresia would probably result. This will explain certain cases. Others may result from intra-uterine misadventure, such as volvulus or intussusception.

The treatment of congenital intestinal atresia lies in surgical measures, although so far the results have not been encouraging.

I wish to express my thanks to the Medical Staff of the Hospital for Sick Children, Great Ormond Street, for permission to make use of the hospital records.

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CONGENITAL DUODENAL STENOSIS DUE TO PERITONEAL BANDS.

BY

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A study of the literature of this subject reveals some confusion of terms, so that it might be well at the outset to define those in common use. Stenosis, or narrowing of the duodenal tube at birth, may arise from:—

(1) Developmental error in the gut itself associated with partial or complete absence of its lumen. This is duodenal atresia.

(2) Compression or constriction of the viscus by abnormal peritoneal bands or adhesions. In this case, the gut itself possesses a normal structure, but its lumen is partially or completely obliterated by the extraneous influences.

The prognosis in these two types may be very different.

The pediatricians of this country should be pleased that by far the finest description and most extensive bibliography on this subject is by Edmund Cautley in the *British Journal of Diseases of Children*[1]. He summarises the literature for the last hundred years and his description of the clinical picture is clearness itself. Ernst of Copenhagen[9] describes a case very like our own with operation and recovery. He, however, performed a duodeno-enterostomy. Other papers on this subject have been published by Jewesbury and Max Page[5], Smellie[6], Marfan[7] and Ritter[2] and excellent observations are made on the whole subject by Cameron[3]. Bosch and Schinz[4] have described the radiographic appearances in this condition.

Case. Baby S., Male, born October 27th, 1925. With the first feed on the second day the vomiting began. The vomit was thin, watery and green in colour. The vomiting was projectile in type, and on the third day was so forceful that it carried as far as the foot of the cot. All the vomits were green in colour. The bowels were open daily. The motions were extremely small, dark olive green in colour, and at first consisted of meconium only but later contained a few undigested curds.

The feeding consisted of half-cream Glaxo for the first week, then whey. The birth weight was 6 pounds 13 ounces. On the 9th day after birth—seen by one of us (D. P.)—the infant was seen to be small and wasted, under nourished, with the "old man" facies so commonly seen in pyloric stenosis. The vomit was seen to be watery and bright green—undoubtedly containing bile. Subcutaneous saline was given and later a feed of bismuth carbonate in milk was administered. Dr. Bertram Shires examined the child by X-rays. The food was seen to pass easily through the pylorus and into the duodenum which ballooned out. It failed to pass further except in very small quantities (*v.* Figs. 1 and 2, for which we are indebted to Dr. Shires). Inspection

showed that the stomach "stood out"; no definite peristaltic waves were noted, but there was a tendency for feeble waves to start, and then fade before they had travelled far across the abdomen. The pylorus could not be palpated although carefully felt for. In view of the clinical picture, the X-ray finding and the history, a diagnosis of duodenal obstruction was made, and the following day the infant was operated on.

The baby having been anæsthetised with N_2O and oxygen, the abdomen was opened by a right paramedian incision over the gastro-duodenal region. The state of affairs then discovered will be appreciated by referring to the drawing (Fig. 3). The stomach and first part of the duodenum were enormously distended. The pylorus could only be localised by the pyloric vein, the stomach and duodenum forming one continuous tube. The pyloric sphincter could not be detected clearly even by palpation. The cause of the duodenal obstruction was found to be the peritoneal bands, which are represented with reasonable accuracy in the drawing. Beyond the site of the duodeno-jejunal junction the gut was collapsed, except for an occasional partially expanded coil. The tethering bands were cautiously snipped through with scissors and it soon became manifest that this procedure had completely relieved the obstruction. The distal coils rapidly ballooned out to a normal size.

Careful examination of the duodenum itself showed no sign of a genuine atresia, although at the spot where the first band began the gut did appear a little narrowed. In view of the fact that the obstruction had been manifestly relieved, the narrowing was not considered of serious account, and the abdomen was closed in the usual way.

The feeding after the operation was much the same as in a case of congenital pyloric stenosis. Hourly feeds of one drachm of Ideal milk mixture were given This was made up of Ideal milk one part, water four parts, demerara sugar one drachm to each four ounces of the mixture. The feed was gradually increased and the interval lengthened until on the fourth day after the operation the normal feed for the infant was reached. The bowels began to act naturally 48 hours after the operation. No vomiting occurred and the child made a rapid and apparently complete recovery. Some months later the infant appeared quite normal.

The interest of these cases lies in the differentiation of them from cases of congenital pyloric stenosis. In them the vomiting, which is projectile, is always definitely bile stained, and invariably begins at birth. Peristalsis is not so well marked and no tumor can be felt. Early diagnosis and surgical treatment are necessary for recovery.

Radiography is a valuable diagnostic asset. If none of the bismuth succeeds in reaching the jejunum we may presume the presence of a complete atresia. In such a case a short circuiting operation will be necessary and the surgeon may find his efforts foiled by an atresia so extensive that no distal loop of bowel can be found with which to make the anastomosis.

Where the bismuth is observed to pass the block, the rapidity and extent to which this occurs should be carefully noted. It may be that the delay is so comparatively slight that operation is not called for, but where the clinical symptoms are at all urgent this is unlikely.

Partial obstruction, while it can occur in true atresia, is more likely to be due to adventitious bands constricting the gut. And such bands, as in this case, may be quite amenable to a comparatively simple surgical procedure. One of us (T. T. H.) has, however, recorded a case[16] where the matting was so extensive that any attempt to free the gut would have been obviously unwise; in this case gastro-enterostomy was performed and proved successful.

It is clear therefore that surgery offers considerable hope in these cases and will practically always be necessary for recovery.

Fig. 1.
Immediately after meal.

Fig. 2.
One hour after meal.

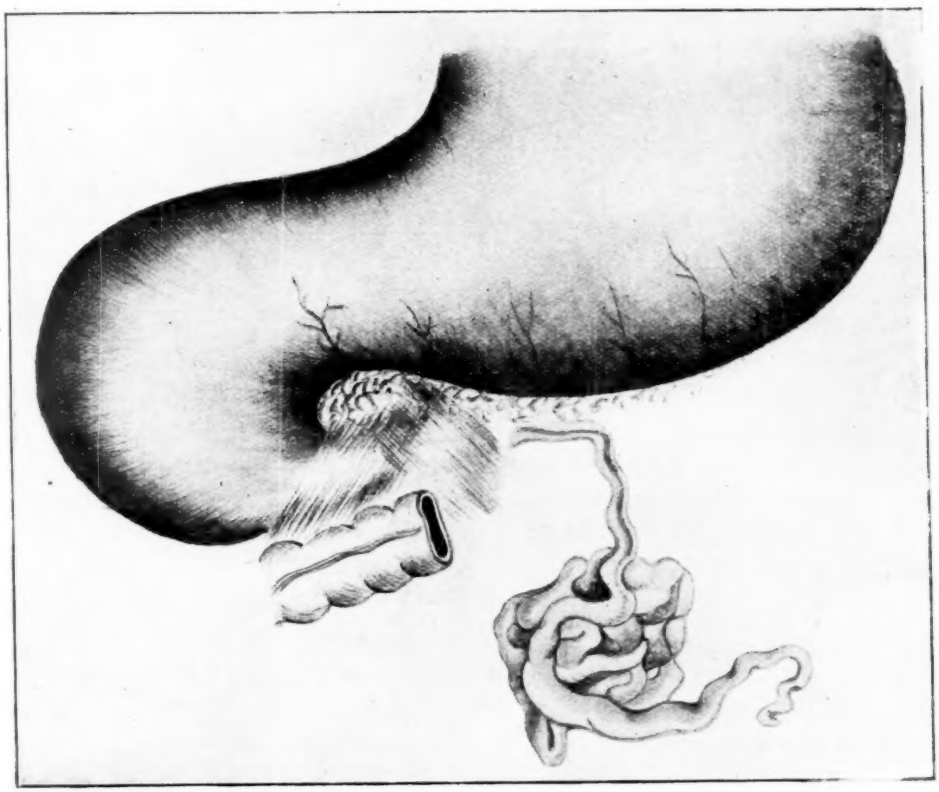

Fig. 3.

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THE DAY-AND-NIGHT CREATININE AND CREATINE IN THE URINE OF INFANTS.

BY

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The difficulties which are encountered in collecting infants' urine quantitatively for satisfactory metabolic periods are well known, and therefore many studies of the urinary constituents in infants have been made on isolated samples collected during short periods. But, as it is possible that the output of these substances may vary from one hour to another, it seemed advisable to make a study of the urine of infants collected in short successive periods throughout the day and night. In this way there would be obtained not only information on the value of results based on fractional collections, but also additions to our knowledge of infant physiology.

In a previous paper[1] I have reported the results of a study of the creatinine excretion in infants. The chief conclusion was that a healthy well-nourished infant excretes, on an average, 10 mg. of creatinine per kilogram of body weight in 24 hours, and thus as an end-product of endogenous protein metabolism creatinine is a constant factor. As a preliminary to any further investigation of creatinine, and for the reasons stated above, it seemed expedient that the day and night elimination of creatinine in infants should be determined in three-hourly periods. And further, in view of the observation that creatine is a normal constituent of the urine of infants (Folin[2] and others) it was also considered important to determine the rate at which this urinary product is excreted.

Owing to the active water exchange the daily urinary output of a healthy infant is normally high, and because of the slight control of the muscles regulating bladder evacuation, micturition in infancy occurs at very frequent intervals. These intervals, however, may not be regular, and the question may be asked if the amount of urine voided during a given short period corresponds to the amount actually excreted by the kidneys. For obvious reasons we did not feel justified in deciding this point by additional catheterisations of the infant at the beginning and end of each period, and our study is based on the samples voided spontaneously. But the high urinary output and the size of the bladder in the infant do not seem to support the idea of long or even appreciable urine retention; and further we hoped by careful selection of the subjects (infants in good nutritional condition and health, of similar habits, feeding and age), and by securing a liberal intake of water, that the results would be satisfactory.

Six healthy male infants between the ages of 5 and 11 months were selected. They all had similar and usual nursing care and were all of the standard feeding of the clinic (whole cow's milk), with the exception of Case 1 which was partially breast-fed. The feeding was uniform for several days before and during the study, and the caloric intake was regulated according to individual requirements.

The experiments were carried out as follows: For the collection of urine infants were immobilised in a comfortable metabolism bed in use in this hospital[3]. Urine samples were collected in three-hourly periods during the day and night, starting at 10 a.m. Following the first day of fractional collections, one total 24 hour collection was employed as a check, comparing the figures obtained for the total daily creatinine output. Urine samples were preserved on ice and by adding toluol. Creatinine measurements were made within 24 hours of the collections of urine, using Folin's[4] colorimetric method. Creatine was converted into creatinine by autoclaving. The results in detail are given in Table I.

The most striking feature of the results shown in Table I. is the remarkable constancy of the findings in all the subjects studied. This justifies the discussion of all the cases together.

Creatinine.—Considering the experimental conditions previously described the three-hourly elimination of creatinine is notably constant in Cases 1, 3 and 5, while it is less so in the other cases. However, even in these instances the variations are much less wide than would be expected from the varying urinary output. Thus in Case 2 the amount of creatinine excreted during the period 10 a.m.-1 p.m. was 8·8 mg. in 58 cc. of urine, while during the following three-hourly period 10·0 mg. of creatinine were found in 304 cc. of urine. Again, in the examples where the variation is more marked the rise or fall in creatinine tends to occur in successive periods. This suggests an overlapping due to imperfect evacuation of the bladder in the periods concerned.

Schaffer[5] has found that the creatinine excretion in adults on a creatinine-free diet is remarkably constant, not only from day to day, but from hour to hour. As our subjects were on a creatinine-free diet a similar result might have been expected as there is no evidence of the presence of any disturbing factor. In this connection it is of interest to mention that in a study of endogenous uric acid excretion in the infant[6] I found it more regular than in the adult. These facts would seem to indicate a remarkable regularity in the endogenous reactions of infant life.

It is evident that the longer the periods of collection of the urine the more closely will the amount evacuated from the bladder correspond to that excreted by the kidneys. Applying this to our results it will be seen that the amounts of creatinine excreted during the day and during the night are equal in Cases 1, 2 and 5; while the other cases fail to show this equality by only 3—4 mg.

TABLE I.—Creatinine and Creatine Excretion in Six Healthy Infants, comparing the Day and Night Amounts in Three-Hourly Periods.

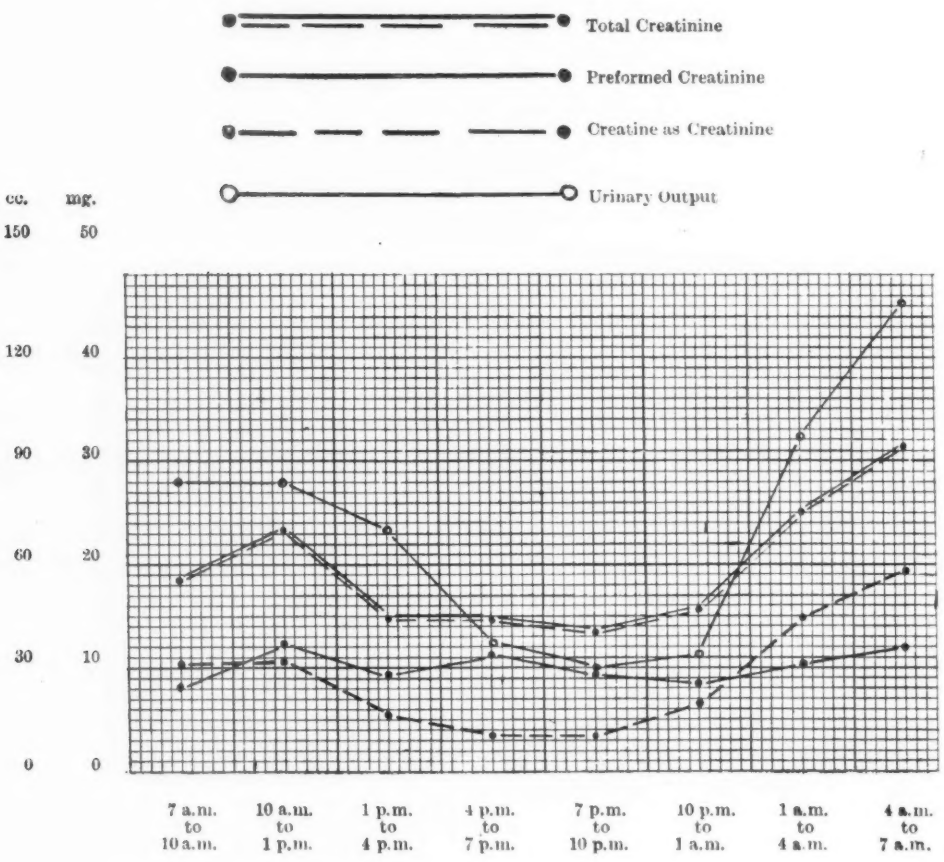
Case. Age. Weight. Day—Month.	Analysis.	First Day: Three-hourly periods.											Second Day. Total in 24 hours.
		Total in 24 hours.	Total		7 a.m.-10 a.m.	10 a.m.-1 p.m.	1 p.m.-4 p.m.	4 p.m.-7 p.m.	7 p.m.-10 p.m.	10 p.m.-1 a.m.	1 a.m.-4 a.m.	4 a.m.-7 a.m.	
			Day	Night									
1. 28 weeks 6·95 kg. 29/30-5 30/31-5	Total Creatinine mg.	155·9	71·1	84·8	18·3	23·5	14·8	14·5	13·2	15·2	25·1	31·3	118·8
	Preformed Creatinine mg. ...	81·1	40·8	40·3	8·0	12·6	9·0	11·2	9·6	8·3	10·3	12·1	76·5
	Creatine as Creatinine mg. ...	74·8	30·3	44·5	10·3	10·9	5·8	3·3	3·6	6·9	14·8	19·2	42·3
	Urine cc.	572	279	293	83	84	75	37	29	33	96	135	385
2. 21 weeks 6·37 kg. 5/6-6 6/7-6	Total Creatinine mg.	168·5	84·9	83·6	20·6	17·6	28·0	18·7	18·8	22·5	13·6	28·7	156·3
	Preformed Creatinine mg. ...	72·8	36·3	36·5	8·9	8·8	11·0	7·6	6·7	10·4	8·2	11·2	67·3
	Creatine as Creatinine mg. ...	95·7	48·6	47·1	11·7	8·8	17·0	11·1	12·1	12·1	5·4	17·5	89·0
	Urine cc.	990	676	314	165	58	304	149	56	75	57	126	1116
3 35 weeks 7·05 kg. 1/2-6 2/3-6	Total Creatinine mg.	230·9	112·2	118·7	31·2	37·6	23·2	20·2	14·0	29·8	33·4	41·5	218·0
	Preformed Creatinine mg. ...	90·4	43·1	47·3	10·2	14·0	10·1	8·8	9·7	11·6	12·1	13·9	96·4
	Creatine as Creatinine mg. ...	140·5	69·1	71·4	21·0	23·6	13·1	11·4	4·3	18·2	21·3	27·6	121·6
	Urine cc.	738	333	405	130	97	71	35	22	102	109	172	690
4. 24 weeks 6·00 kg. 9/10-6 10/11-6	Total Creatinine mg.	172·8	91·1	81·7	16·7	33·4	10·2	30·8	18·2	19·8	18·5	25·2	184·4
	Preformed Creatinine mg. ...	67·1	35·3	31·8	7·0	11·9	6·5	9·9	6·2	7·5	8·6	9·5	70·2
	Creatine as Creatinine mg. ...	105·7	55·8	49·9	9·7	21·5	3·7	20·9	12·0	12·3	9·9	15·7	114·2
	Urine cc.	540	254	286	76	85	26	67	66	45	65	110	586
5. 37 weeks 6·95 kg. 24/25-6 25/26-6	Total Creatinine mg.	191·6	91·9	99·7	14·9	21·7	28·7	26·6	27·2	24·6	24·3	23·6	184·8
	Preformed Creatinine mg. ...	89·6	44·9	44·7	8·6	13·7	10·1	12·5	12·4	12·9	9·8	9·6	92·4
	Creatine as Creatinine mg. ...	102·0	47·0	55·0	6·3	8·0	18·6	14·1	14·8	11·7	14·5	14·0	92·4
	Urine cc.	897	346	551	53	72	125	96	98	104	169	162	785
6. 48 weeks 7·0 kg. 20/21-6 21/22-6	Total Creatinine mg.	213·8	109·9	103·9	41·2	23·0	24·2	21·5	28·0	18·0	40·8	17·1	201·6
	Preformed Creatinine mg. ...	83·6	43·2	40·2	15·6	10·5	9·9	7·2	9·0	12·7	12·6	6·1	80·6
	Creatine as Creatinine mg. ...	130·2	66·7	63·5	25·6	12·5	14·3	14·3	19·0	5·3	28·2	11·0	121·0
	Urine cc.	794	413	381	145	106	110	52	97	70	169	45	723

It is well known that adults normally excrete more creatinine during the day than during the night, a fact which has been attributed by different observers[7] to varying muscular tonus. The above findings in the infant might lend some support to this theory, since in them the mode of life as regards sleep and muscular tonus is the same by day and by night. It is possible, of course, on the assumption that creatinine is purely a waste product and has no value in synthetic processes, as suggested to me by Professor Cathcart, that there may be in the adult during the day time increased anabolic changes, leading to a more rapid throwing out of effete tissue. If this be the explanation then the results would point to a greater uniformity in the diurnal and nocturnal metabolic processes in the case of the infant.

Creatine.—In all our cases the curve showing the three-hourly creatine elimination is markedly irregular and almost invariably parallel to the urinary output, which would appear to be at least the chief determining factor.

CHART I.

Showing excretion of Creatinine, Creatine (in mgs.) and Urine (in ccs.) in three-hourly periods during the day and night.



In this connection it is interesting to record that Fowler and Howk[8] studying water-drinking in a male adult found that creatine, which is normally absent from the urine of male adults, appeared after the ingestion of large amounts of water. They explained this phenomenon by the increased catabolism of protein induced by the increased intake of water, the subsequent " flushing-out process " removing end-products from the body tissues. The variations of creatine output are best illustrated by the following chart, which represents graphically the findings in Case 1.

The origin of creatinuria in infancy and childhood is a question of great interest and no little difficulty. In the normal adult creatinuria depends wholly on the diet and is thus considered exogenous in origin, whereas in the infant, owing to the general belief that milk is creatine-free, the creatinuria during this period of life has been usually assumed to be endogenous in origin. It has been shown by Gamble and Goldschmidt[9], however, that a higher creatine output resulted when the infant's diet consisted of whole milk, than when the diet consisted of milk from which the whey was removed, and they concluded that creatine of exogenous origin was thus an important factor in the creatinuria of infants. Folin[10] has demonstrated that large amounts of creatine may be ingested by a normal adult man without any appearing in the urine, and Gamble and his co-worker[11] have shown that creatine ingested by infants may be excreted quantitatively. It would thus appear that not only the presence of creatine in milk but also the varying ability of the infant to metabolise creatine are concerned in both the appearance of creatine in the urine of the infant and its irregular excretion as shown in our results. It is worthy of note that the total output of creatine during 24 hours in our cases approaches the total creatinine output, and that the amounts of creatine excreted by day and by night are roughly equal.

Conclusions.

(1) In the healthy infant the rate at which creatine is excreted as judged by three-hourly periods is fairly constant; this constancy becomes more marked when expressed in day and night ratios. The amount of creatinine excreted is independent of the volume of urine voided.

Two explanations, both hypothetical, are offered for the above stated facts, viz.:—Uniformity of muscular tonus and uniformity of anabolic processes in the infant during the day and night.

(2) Creatine output is irregular and is closely related to the volume of urine passed.

Three factors are suggested in explanation of this phenomenon: (a) the " flushing-out process " due to the high water intake of the infant; (b) the presence of exogenous creatine in cow's milk; and (c) the inability of the infant to metabolise creatine.

(3) On the basis of the findings in this study it would appear that creatinine estimations for clinical purposes may be done on the basis of collections over short periods, but in the case of creatine studies over longer periods are essential.

I desire to express my gratitude to Professor Leonard Findlay and to Professor E. P. Cathcart for their kind help and suggestions.

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TUBERCULOUS DACTYLITIS IN INFANCY.

BY

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Tuberculous dactylitis, though not one of the commoner tuberculous lesions, is frequently seen in young children of the class who attend a Hospital Out-Patient Department. It is, however, rare to see adults with scars or deformity resulting from this lesion. We were so much struck by this fact that we thought it would be interesting to try to ascertain the end results of treatment of tuberculous dactylitis in infancy.

In the five years from 1920 to 1924 inclusive, 1,403 patients suffering from tuberculosis attended the Surgical Out-Patient Department of the Royal Edinburgh Hospital for Sick Children, and of these 97 had tuberculous dactylitis, representing 6% of all cases of surgical tuberculosis.

We have had great difficulty in tracing our cases. Many of them are the children of the very poor, who have no fixed homes, and who disappear completely as soon as they stop attending hospital. We have, however, been able to collect a series of 60 cases which illustrate some points of interest.

Pathogenesis.

As in other forms of tuberculosis, ætiology and pathology are of the greatest importance, and we therefore venture to go over some familiar ground. It is generally accepted that tuberculous dactylitis is a secondary manifestation and that the infection is blood borne. Much careful research by Stiles, Fraser and Mitchell in Edinburgh, and workers in other countries has established the fact that many young children are infected by drinking unboiled milk from tuberculous cows so that the infection is a bovine one.

Working in a busy Out-Patient Department it was impossible to investigate all our cases in order to ascertain whether the infection was human or bovine, but it is often possible to get a rough idea from the history. Seven of our patients were living with adults known to be suffering from active phthisis; in these instances the infection was probably human. Nearly all the other cases had been fed, in part at least, on unboiled cow's milk, and the infection may be regarded as bovine.

The route by which the tubercle bacillus reaches the position where the obvious focus of infection appears, has also been widely discussed. It is known that the tubercle bacillus can pass through the apparently normal mucous membrane without leaving any trace of its passage. This is what commonly occurs when the bacilli are ingested, and it seems that the weak points in the alimentary canal where the tubercle bacilli most frequently pass through are the tonsils and the lymphatic tissue at the lower end of the ileum. Having passed through the mucous membrane, the bacilli enter the lymphatics, and are carried to the glands where they are probably always arrested. Here the organisms may be destroyed by the natural resistance of the tissues, or they may multiply. The result in a short time is a typical primary focus situated in one of the ileocæcal lymphatic glands. This focus may still be overcome and we know how frequently the presence of fibrosed or calcified glands without other evidence of tuberculosis shows that this has occurred. On the other hand, the focus may extend rapidly and the gland breaking down, the disease begins to spread.

Often this spread is local and how common this is appears from the fact that tuberculosis of the cervical glands due to spread from the tonsils or lymphoid tissue of the pharynx constitutes 62% of our cases of surgical tuberculosis, and tuberculosis of the mesenteric glands about 8%. Regarding this latter figure it must be remembered that, unless complicated, most cases of abdominal tuberculosis are treated on the medical side of the Hospital.

At any moment a blood vessel may become involved in the tuberculous process and through the damaged vessel wall the tubercle bacilli gain access to the blood stream, and the infection now becomes generalised.

The bacilli may be arrested at any point, but as Fraser has pointed out, the distribution of the blood supply to the growing bones of children makes it easy for the bacilli to be held up at certain definite points.

A list of the various bones and joints affected in our series of 1,403 cases of surgical tuberculosis may be given here:—

Bones.

Small bones of hands or feet	97
Spine	73
Tibia	13
Ribs	9
Malar	6
Mandible	5
Radius or Ulna	5
Tarsus	3
Femur	1
Fibula	1
	213

Joints.

Hip	93
Knee	66
Ankle	29
Shoulder	6
Elbow	7
	201

We find, then, that the small bones of the hand or foot are affected in 6% of all our cases of surgical tuberculosis, and we have gone carefully into the route of infection so as to emphasize the fact that the bacillus must reach the extremities through the blood stream.

It often happens that a mother comes up to consult a doctor with the feeling that a tiny swelling on her baby's toe is hardly worth troubling about; or it may be that a fusiform swelling of a finger is discovered while the infant is being examined for some other reason. These children, however, have had tubercle bacilli circulating in the blood and a tuberculous meningitis may be the next manifestation.

Every case of tuberculous dactylitis then must be regarded as serious and treated with the greatest care. The parents should be told that treatment must be persevered in until the doctor is satisfied that the lesions are completely healed, however long this may take.

Clinical Diagnosis.

Clinically these cases are not difficult to diagnose. Occasionally, as already mentioned, the condition is discovered accidentally, but usually the child is brought to the doctor with the history that there has been a painless swelling in the hand or foot of some weeks' duration.

On examination there is found to be either the typical fusiform swelling of a finger or toe, or a diffuse swelling on the dorsum of the hand or foot according to whether a phalanx, a metacarpal or a metatarsal is involved. Sometimes an abscess has formed, with discoloration of the skin and fluctuation, and this may have burst or have been incised, leaving a discharging sinus. Unless there has been a secondary infection there is only slight tenderness and practically no pain or heat, but the part may appear red and glazed. Where secondary infection of a sinus has occurred the condition closely resembles a sub-acute osteomyelitis of pyogenic origin.

The child generally uses the affected hand or foot quite freely, and unless there are complications, appears to be in good health.

Both hands and both feet should always be carefully examined as these lesions are frequently multiple. In our series of cases, 40 showed multiple bone lesions. Many of these children have also small foci of tuberculosis in the skin, evidenced by localised thickening, with possible fluctuation and discoloration.

An X-ray photograph of a typical case shows expansion and rarefaction of the bone often with a formation of new subperiostal bone. The entire phalanx or metatarsal is usually involved, the disease being of the infiltrating variety. It is not common to find that the epiphysis is involved, but the disease may spread through the end of the bone where there is no epiphysis, into the neighbouring joint.

There is sometimes a history of slight injury, but we only obtained this in six of our cases, and this is only of importance in that it may delay the diagnosis.

The age of the child varies, but the disease is essentially one of the first year of life, as the following table shows:—

Age in Years.	*Number of Cases.*
Under 1	14
1—2	24
2—3	7
3—4	5
4—5	5
Over 5	7
	60

Treatment.

(i) *Local Conservative Treatment.*—Immobilisation as in other forms of bone tubercle is the first principle of local conservative treatment, and this is obtained in various ways.

For the hand, the most useful splint is a flat piece of aluminium cut to an oval shape broad enough for the whole hand to rest on, and extending from the tips of the fingers almost to the elbow. The splint is covered with boracic lint, and the hand, with cotton wool between the fingers, is firmly strapped on with adhesive plaster and further secured by a bandage. The splint should be changed once a week, and it is not advisable to allow the mother to do this herself.

For the foot, plaster of Paris is often useful, and good results may also be obtained by strapping the foot into a Jones' Talipes Splint, which also allows of a dressing, should a sinus be present.

(ii) *General Conservative Treatment.*—This is simply that for tuberculosis in any part of the body, and for older children a long stay in a sanatorium may work wonders. Babies on the whole are better at home, and with careful attention to diet and plenty of fresh air, often do very well. Cod liver oil may be prescribed and the syrup of the iodide of iron is useful. We have recently tried the effect of artificial sunlight from an arc lamp on one or two cases and the results, though naturally inconclusive, are distinctly encouraging.

The question of the use of Tuberculin is one which must be decided on the merits of each individual case. We have used it frequently both in the form of hypodermic injections and of Moro's ointment, and have not been able to convince ourselves that the cases who had this treatment did any better than those who did not.

(iii) *Operative Treatment.*—(*a*) It will be necessary to open and scrape an abcess when the skin is already infected or on the point of breaking down. This practically always results in a sinus, but has the advantage of removing the tuberculous granulation tissue and the pyogenic membrane of the abcess wall. This should be done through a small incision preferably in healthy skin which is afterwards closed by a stitch. Where a sinus is already present, it is naturally not advisable to risk forming another sinus in healthy skin.

(*b*) The abscess and the track leading to the bone may be more freely exposed and the bone debris deliberately scraped out with a sharp spoon. These two methods merge into one another and in either case no drain should be inserted.

(*c*) Where there is no superficial abscess subperiosteal resection of the affected bone is theoretically the ideal method of treatment, but in practice it does not answer so well. The wound may heal by first intention, but frequently a week or so later it breaks down and results in a troublesome sinus, and in many cases there may result considerable shortening of the affected finger or toe. The method is mainly applicable to metacarpal and metatarsal disease.

(*d*) Amputation should be carried out only when a single phalanx is affected and it must always be well above the disease, or there will be recurrence in the scar.

Whether conservative or operative treatment gives the best result in surgical tuberculosis is very debatable, but in tuberculous dactylitis the main question in deciding between the various methods is that of the ultimate function of the part. The importance of function in the hand cannot be over-estimated, so we have made it a rule never to interfere with a hand unless we are convinced that the disease will cause as much loss of function as will our operative treatment.

In the foot, operation is probably more often justified, but in any case conservative treatment should be uppermost in the mind when considering a case of tuberculous dactylitis.

In our series we operated on 24 cases. The operations consisted of ten amputations, two subperiosteal resections, and in the remainder opening and curetting. Seven of the 24 cases had more than one operation.

Complications.

Unfortunately, as is to be expected where we have an infection of the blood stream with tuberculosis, these cases are often complicated by the appearance of tuberculous foci elsewhere. The following table shows what complications we should be on the lookout for, and also gives the length of time which intervened between the diagnosis of tuberculous dactylitis and the appearance of the other foci.

This table shows that out of our 60 cases, 29 had complications, many of a serious nature, but that in spite of this the results are encouraging and most of the children are doing well. Only one death has been recorded.

TABLE SHOWING TUBERCULOUS COMPLICATIONS IN 60 CASES OF TUBERCULOUS DACTYLITIS.

Age.	Date when first seen.	Date of complication.	Site of complication.	Result.
8/12	2/4/21	25/1/22	Synovitis of knee and skin foci	Child very well but has partial backward displacement of knee, and two deformed fingers
9/12	18/3/22	18/3/22	Focus in right humerus and skin foci	Cured. One finger amputated
1 4/12	12/4/21	9/6/21	Kidney	Kidney excised. Child now very well
3½ yrs.	26/5/22	3/10/22	Focus in upper end of right tibia	Cured
*7 yrs.	18/6/24	18/6/24	Right elbow	Much improved. Epitrochlear gland removed recently
4 yrs.	3/4/23	3/4/23	Cervical glands	Cured. Operation for glands
1 9/12	16/2/21	16/2/21	Cervical glands	Much better. Recently had trouble with glands
10/12	2/5/22	2/5 22	Extensive skin lesion of hand and arm and disease in metacarpal bone	Cured. Sunlight
11/12	31/8/23	6/6/24	Cervical glands	Cured. Operation for glands
8/12	14/6/21	14/6/21	Cervical glands epitrochlear gland and ankle joint	Cured
1 5/12	21/3/22	21/4/22	Temporal bone	Improved. Sinus still present when last seen
1 4/12	1/12/23	1/12/23	Cervical glands and abdominal gland	Improved. Still in a sanatorium
10/12	8/1/23	23/4/23	Malar bone	Better. Still in sanatorium

*Note.—Treated for dactylitis elsewhere before seen by us.

TABLE SHOWING TUBERCULOUS COMPLICATIONS—*continued.*

Age.	Date when first seen.	Date of complication.	Site of complication.	Result.
2 yrs.	2/7/23	2/7/23	Abdomen	Cured
$2\frac{1}{12}$	29/4/24	26/5/24	Multiple skin foci	Bad case requiring several operations. Now much better
$1\frac{1}{2}$	1/6/23	1/6/23	Multiple skin foci	Cured
$1\frac{1}{12}$	7/1/24	20/6/24	Epitrochlear gland	Improved. Discharging sinus at elbow
3 yrs.	17/7/23	28/3/24	Cervical glands	Improved. Still has sinus on hand and on neck
$3\frac{1}{2}$	6/2/24	3/3/25	Cervical glands	Improved. Still has sinuses
$1\frac{1}{12}$	17/3/22	31/3/22	Ulna	Better. Still in sanatorium
$1\frac{4}{12}$	20/4/22	30/4/23	Cervical spine	Much better. Still on frame, but lesion nearly healed
$1\frac{2}{12}$	21/2/22	21/2/22	Shoulder	Cured. Shoulder ankylosed
$1\frac{7}{12}$	17/5/21	28/6/21	Cervical glands	Cured
*6 yrs.	17/2/22	21/?/22	Femur	Improving. Still has Thomas walking Calliper
$1\frac{8}{12}$	3/3/19	15/1/20	Mastoid	Died
$1\frac{6}{12}$	30/3/19	1/2/20	Testicle	Cured. Operation for testicle
5 yrs.	20/11/19	22/12/21	Cervical glands	Cured. Bad scar
$\frac{8}{12}$	20/3/24	20/3/24	Mastoid	Improved—facial paralysis
1 yr.	21/6/24	23/8/24	Dorsal spine	Still on frame but improving

**Note.*—Treated for dactylitis elsewhere before seen by us.

Conclusions.

Tuberculous dactylitis, being a blood borne infection, must always be regarded seriously.

Much patience is required as the treatment may have to be continued for years, but in nearly every case we have the satisfaction, despite complications, of seeing the children recover.

Except in severe cases recovery is often so complete that it is difficult to be certain where the lesion was.

KETONÆMIA AND KETONURIA IN CHILDHOOD.

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The formation of ketone bodies and their excretion in the urine in abnormal amounts have for many years been problems of much interest to both physiologist and clinician. Much of our present knowledge of the subject has been gained from the study of carbohydrate metabolism in diabetes, where ketonuria in its classical form is frequently observed. From this it has been established that an excess of ketone bodies occurs in the blood when the fats are incompletely 'combusted' as a result of abnormal carbohydrate metabolism, and ample justification has been provided for the well-known statement made by Rosenfeld[1] in 1895 'that fat burns only in the fire of carbohydrate.'

A good review of our present knowledge of ketone production and its prevention is to be found in Shaffer's recent lecture entitled 'Antiketogenesis, its Mechanism and Significance.'[2] A full discussion of the subject in all its aspects is not within the scope of the present communication, but we may quote Shaffer's statement that 'there is to-day no question that ketosis is due to carbohydrate starvation,' and make special reference also to his reminder that the inhibitory effect of carbohydrate on ketone formation depends, not on the mere existence of sufficient glucose, as glucose in the blood (*cf.* diabetes), but on the presence of a sufficient amount of an oxidation product of glucose which reacts with one of the acetone bodies or its precursors. That ketosis has long been known to occur during fasting supports the view that it is due to the faulty combustion of fats in the absence of carbohydrate; for the first of the body reserves available is fat, which is then burned in the absence of sufficient glucose for its complete oxidation.

I.—THE CLINICAL SIGNIFICANCE OF KETONURIA.

Clinical interest in the subject has recently been stimulated, and a demand for further investigation made, by the fact that the excretion of abnormal amounts of ketone bodies in the urine is a frequent accompaniment of mild infections in childhood. Ketonuria has been found to occur in a fairly large percentage of hospital patients, irrespective of the disease for which they were admitted.

Garland[3], for instance, in 734 cases admitted to the children's wards of the Massachusetts General Hospital, found acetonuria in 17·3%, though in only two of these was there definite evidence of acidosis. Howard[4] found acetone bodies in the

urine in 18% of 171 children examined, and Smith (5) in a survey of 37 cases, reported acetonuria in 13%. Much higher percentages have, however, been published by Holt(6) in New York and by Frew(7) in London. The former gives 30 as the percentage of infants who gave evidence of acetone in the urine out of 200 consecutive cases which he examined on admission to hospital; while Frew found that 61·2% of 662 children admitted showed ketonuria.

Our experience confirms the higher percentages of Frew, as in 300 children admitted to the wards of this hospital we have found that acetone bodies were present in the urine of 54·7%.

The frequency with which acetonuria accompanies disease in childhood was probably responsible for the following comment made by Howland and Marriott(8) in 1915: ' It has been assumed that the acetone bodies are very abnormal and that their presence signifies an unusual complication in the course of the disease, whereas, in many instances, we may liken the mere presence of acetonuria to fever, for it occurs in most of the infectious diseases of childhood with much the same regularity that fever does.' In consequence of this much quoted statement it has come to be recognised that the acetonuria occurring in the diseases of childhood may be of little significance and may require no special treatment. This, however, in no way advances our knowledge of its causation.

Many theories have been propounded to explain the abnormal excretion of ketone bodies, but, broadly speaking, these can be resolved into three main groups as follows:—

(1) That the ketonuria is caused by the effect of fever on the metabolism.

(2) That ketonuria is due to partial deprivation of carbohydrate resulting from temporary anorexia.

(3) That ketonuria is the result of the psychic disturbances associated with admission to hospital wards.

The first of these theories appears to be well supported by the fact that the published figures for the incidence of ketonuria are much higher in febrile patients than in those without fever. Reiche(9) found that out of 3,200 patients with diphtheria, acetone bodies were present in the urine of 65%. Proskauer(10) found acetone in the urine of 100 scarlet-fever patients at some time during the illness and attributed it to carbohydrate inanition, the result of toxic influences. Holt's(6) figure of 70% for patients with lobar pneumonia is much higher than that given by him for the series of miscellaneous cases, while Harris(11) gives the startling figure of 85% to represent the incidence of ketonuria in scarlet-fever patients and 90% in diphtheria patients, of whom he examined 197 and 96 respectively. Veeder and Johnstone(12), however, who estimated quantitatively the amount of the acetone bodies in the urine of 41 cases of infectious diseases, concluded that the presence of acetone in 58% was in no way connected with the severity of the infection nor with the degree of fever. They also concluded from further investigation that the decreased intake of food could not wholly explain the increase of acetone bodies in the urine and assumed that psychic influences played a large part in its causation.

It is important to remember that ketone production can result only from the burning of fat in the absence of sufficient carbohydrate, a state of affairs which may come about in any one of the three ways mentioned above. In fact, each of the suggested factors resolves itself into a relative

or absolute carbohydrate deficiency, and the crux of the problem is to determine which of the three possible factors is responsible for producing this.

Fever may cause relative glucose deficiency by too rapid burning of body fat with which even the combustion of normal amounts of carbohydrate is unable to cope. On the other hand, fever may induce an unduly rapid utilisation of the carbohydrate store, causing a temporary insufficiency which may be further accentuated by a diminished carbohydrate intake.

Anorexia without fever may result in carbohydrate starvation, while psychic influences may lead either to reduced carbohydrate intake or to faulty carbohydrate metabolism, which is undoubtedly influenced by the nervous system. Keeping all these facts in view we have tabulated our results according to the presence of fever, and to the age of the children. The latter classification was adopted on the ground that children over two years would be likely to suffer from a greater degree of psychic upset than those under this age, and we hoped, by this means to come to some conclusion regarding the importance of the mental strain of admission to hospital as a factor in the production of ketonuria.

TABLE I.

	Number of cases examined.	Number giving a positive test for acetone	Percentage giving a positive test for acetone.
All cases	300	164	54·7
Febrile patients	119	71	59·6
Afebrile patients ...	180	93	51·7
Patients over 2 years ...	169	99	58·5
Patients under 2 years ...	130	65	50·0

The results shown in Table I. do not reveal as great a difference between the febrile and afebrile groups as might have been expected from the figures of other workers already quoted. It is also seen that although children under 2 years of age suffered less frequently from acetonuria, whether they were fevered or not, the difference in percentages is hardly sufficient to support the view that the condition chiefly results from psychic disturbances. Investigation along these lines has therefore, in our hands at least, proved disappointing. To us it appears that, in each patient, any or all of the various factors may play a part in the production of carbohydrate deficiency and the consequent ketonuria.

At the same time we may point out that amongst our patients high continued fever is frequently met with in which no acetonuria appears and it would therefore seem unlikely that fever *per se* exerts a specific action leading

to derangement of carbohydrate metabolism. We have also been able to show that in an afebrile child whose urine was examined every two hours, complete deprivation of food may exist for 24 hours without the appearance of acetone in the urine as demonstrated by Rothera's test. It is evident from these results, and others quoted below, that the ketogenic reaction to carbohydrate deficiency in different children may vary considerably, not only in the rapidity of its production, but also in its severity: yet it is unlikely that the short partial deprivation of carbohydrate experienced by the ailing child is sufficient, of itself, to produce ketonuria to the degree occasionally met with in hospital practice.

From a general survey of all the opinions to be found in the literature it must be admitted that the cause of the abnormal excretion of ketone bodies has been the subject of much speculation, but that little definite information on the point has emerged. The possibilities of making any real advance in our knowledge are small while there remain unsolved the following problems:—First, the relationship of the amount of ketone acids in the blood to their appearance in the urine; secondly, the point beyond which the accumulation of these acids becomes dangerous; and thirdly, the criteria by which a serious may be distinguished from a negligible ketonuria.

II.—THE RELATIONSHIP OF ACIDOSIS TO KETOSIS.

Although much difference of opinion has existed with regard to the limitations of each of these terms (acidosis and ketosis) the accepted view now appears to be that the term acidosis should be applied only to the condition in which there is a definite shift of the acid-base balance of the blood to the acid side beyond the limits of normal variation. That such a change does not readily occur is to be expected from the fact that Nature has very generously provided for considerable variation in acid intake and acid production by the following mechanisms:—

(1) The excretion of excess CO_2 and volatile acids *via* the lungs.

(2) Changes in the base-binding properties of the blood cells according to whether the hæmoglobin is oxygenated or reduced.

(3) Excretion of excess of non-volatile acids by the kidneys.

(4) The buffer action of the blood salts.

By these four means the actual hydrogen-ion concentration of the body fluids is kept within what are probably very narrow normal limits. Hence acidosis, in the true sense of the term, should only occur when damage to, or relative under-action of, one of these mechanisms is superimposed upon the over-production or over-absorption of acids such as the ketone bodies.

The danger point in ketone production is universally admitted to be the commencement of an acidosis, but much controversy exists as to the best method of detecting the presence of this condition in its early stages. While several reliable methods for the purpose are available to the physiologist, even the simplest of these is in most cases inaccessible to the clinician in his ordinary work. Measurement of the alveolar CO_2 from which the alkalinity of the blood may be calculated, always difficult and doubtfully reliable, is

specially so in the child. Changes in the hydrogen-ion concentration of the blood as demonstrable by the simpler methods now available, can only be obtained in the presence of an acidosis so severe as to be easily recognised clinically. In our hands it has not been possible to demonstrate any marked change in the pH by the method of Dale and Evans[13], even in cases where all the recognised signs of clinical acidosis were present.

The only practical methods left to us for judging the severity of a ketonæmia are therefore the CO_2-combining power of the blood ('alkaline reserve'), and the actual measurement of the acid suspected to be the cause of the disturbance. It was partly with the object of attempting to show some connection between these two latter factors that the present investigation was undertaken.

By making use of the present knowledge of ketogenesis and anti-ketogenesis it has been found possible to classify the commoner foodstuffs according to their ability to produce or to inhibit the production of ketone acids. Thus each of the proximate principles is known to contain roughly a constant number of ketogenic and antiketogenic units, and a diet containing an excess of ketogenic units can be depended upon to produce an excess of ketone acids in the course of its combustion. Such an acid-producing diet has been employed therapeutically, chiefly in America, for the treatment of epilepsy and an admirable opportunity has thus presented itself for the study of the factors associated with the production of ketone bodies in the blood, their relation to the blood sugar, and their effect on the acid-base balance of the body. It was hoped that the present study would give further confirmation of the results so obtained and throw some light on the responses of ketonæmia to various forms of treatment.

Methods.—The children who were the subjects of investigation were for the most part epileptics of between 6 and 12 years of age. In each case, after a few days on general diet, the alkaline reserve, blood acetone, and blood sugar were determined. The patient was then given a ketogenic diet consisting of fat bacon, butter, cream, and diabetic rolls. By this means 5 grammes of fat and 0·2 grammes of carbohydrate were consumed for every gramme of protein, the proximate principles thus being supplied in the following proportions:—*fat*, 25; *protein*, 5; *carbohydrate*, 1. The actual amounts of each item of diet were varied slightly according to the age of the child but the proportions were in all cases roughly the same. During the experiment all the patients except one were kept at rest in bed, and the diet supplied contained on an average 600 to 700 calories more than the calculated basal requirement. Nevertheless, all the children except two lost weight slightly, though they took the diet well and complained only of the excessive amount of butter which had to be consumed with each roll.

The daily quantities of urine were collected and the total acetone bodies estimated and stated in terms of grammes of acetone per litre. Where possible the amount of urine passed during the 24 hours was accurately measured and the total amount of acetone excreted in the 24 hours calculated. Blood-acetone and alkaline-reserve estimations were made at intervals during the period on the ketogenic diet and in several cases the blood sugar was also estimated. The figures for blood acetone represent the total acetone bodies in grammes of acetone per litre as obtained by the Van Slyke method[14]. The alkaline reserve was estimated by means of the Van Slyke[15] apparatus, duplicate estimations being made in each case. MacLean's[16] method was

used for estimating the percentage of sugar in the blood, each estimation being preceded by a fast of at least three hours. After varying periods, treatment for combating the ketonuria was instituted and the behaviour of the acetone in the blood and urine, and of the alkaline reserve watched for a further period of several days.

In all 14 studies were made. Details of the various studies are given in Tables III. to VI., and one result from each class of experiment graphically represented in Charts I. to IV.

Discussion of Results.

(i.) *Acetone in Blood and Urine.*

Although figures for the concentration of the acetone bodies in normal blood and urine are already available in the literature, we have found it exceedingly difficult to obtain from them an idea of the average normal amount, because the various workers have employed not only different methods, but also different terms for the expression of their final results.

The results collected from the literature are given in the following table:—

TABLE II.

Amount of Blood Acetone and Urine Acetone in Healthy Children According to Various Authors.

Authors	Method	Blood: result expressed in mgms. % in terms of			Urine: result expressed in mgms. % in terms of acetone
		Acetone	Acetone & Aceto-acetic acid	Oxybutyric acid	
Hubbard and Novack (17)	Modification of Messinger	0 to 0·3	..	...	0 to 1·2
Marriott (18) ...	Modification of Shaffer	0·5 to 1·5	...	...	...
Veeder and Johnstone (19)	Shaffer... ...	...	...	...	50 to 80 mgms. per diem
Marfan (20) ...	Not given ...	...	...	...	30 to 80 mgms. per diem
Jeans and Johnstone (21)	Marriott's ...	10	...	...	...
Moore '22) ...	Marriott's ...	0·8 to 1·3	...	...	...
Hubbard (23) ...	Hubbard ...	...	0·41	0·8	...
Van Slyke (14)...	Van Slyke ...	1·3 to 2·8	...	...	2·8
Brown & Graham (Present communication)	Van Slyke ...	0 to 1·7	...	...	0 to 1·7

It would appear from the figures given in Table II. that the total acetone bodies of the blood when expressed in mgms per 100 cc. may vary from 0 to 15 (0 to 0·15 grms. per litre).

Marriott's[18] and Moore's[22] results, which were both obtained by the same method, agree very well, and when combined give a normal variation for children of from 0·005 to 0·15 gms. per litre. Our figures obtained by the Van Slyke method showed a much smaller range of variation (0 to 0·017 gms. per litre) in 19 normal children, and are in keeping with the results obtained in adults by the originator of the method. This variation of the results according to the method employed shows the necessity for the establishment by each worker of his own normal figures. From our study we conclude that with the Van Slyke method any figure over 0·020 gms. per litre is abnormally high. It would also seem that individual variations over very prolonged periods are not inconsiderable, for one patient on a general diet showed the following variations in the blood acetone figures from time to time:—

Case No.	November 6th	...	0·006 gms. per litre.
	,, 24th	...	0·018 ,, ,, ,,
	December 3rd	...	0·009 ,, ,, ,,

Our results show clearly that the administration of a ketogenic diet causes in every case a rapid increase of the acetone bodies in the blood. In the one patient (Case No. 11) whose blood was examined daily, the rise was apparent after 24 hours on a high fat diet and continued with one negligible remission till the eighth day when it began to show a slight spontaneous fall. This is in accordance with the results in fasting obtained by other workers. Labbé and Nepveux, for example, state that after a maximum period of seven days the acetone bodies tend to disappear spontaneously though the fasting is continued. It would seem, therefore, that after some days the metabolism is able to adjust itself partially to the lack of carbohydrate.

A closer study of all the figures has revealed the fact that a ketogenic diet may produce an increase in the blood acetone of anything from 2 to 40 times the normal amount. For example, Case No. 7 whose blood acetone was 0·001 gms. per litre at the beginning of the experiment had 0·041 gms. per litre on the sixth day of the ketogenic period; while Case No. 1, a child of the same age and on the same diet, began the experiment with 0·015 gms. per litre and on the sixth day had only 0·022 gms. The factors which determine the severity of the reactions to the ketogenic diet are not apparent, but probably are connected in some way with variations in metabolic rate.

When an increase in the blood acetone was obtained, due either to starvation or to a ketogenic diet, the ketonuria was also markedly increased and the figures show a rough parallelism. The correspondence between the figures is not close, yet they seem to justify the general conclusion that increase in the urinary acetone indicates undoubted increase in the blood acetone, though this may be only slight. In none of the cases have acetone

bodies appeared in the urine without some increase in the acetone bodies in the blood.

It is of interest to note that in no case has the presence of even marked ketonuria and ketonæmia had a diuretic effect. Blood and urine may contain

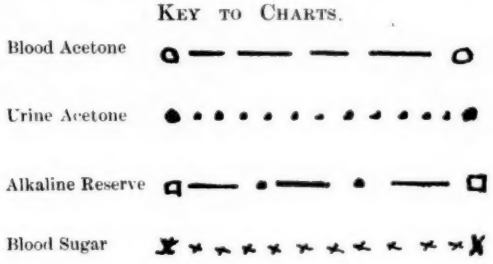
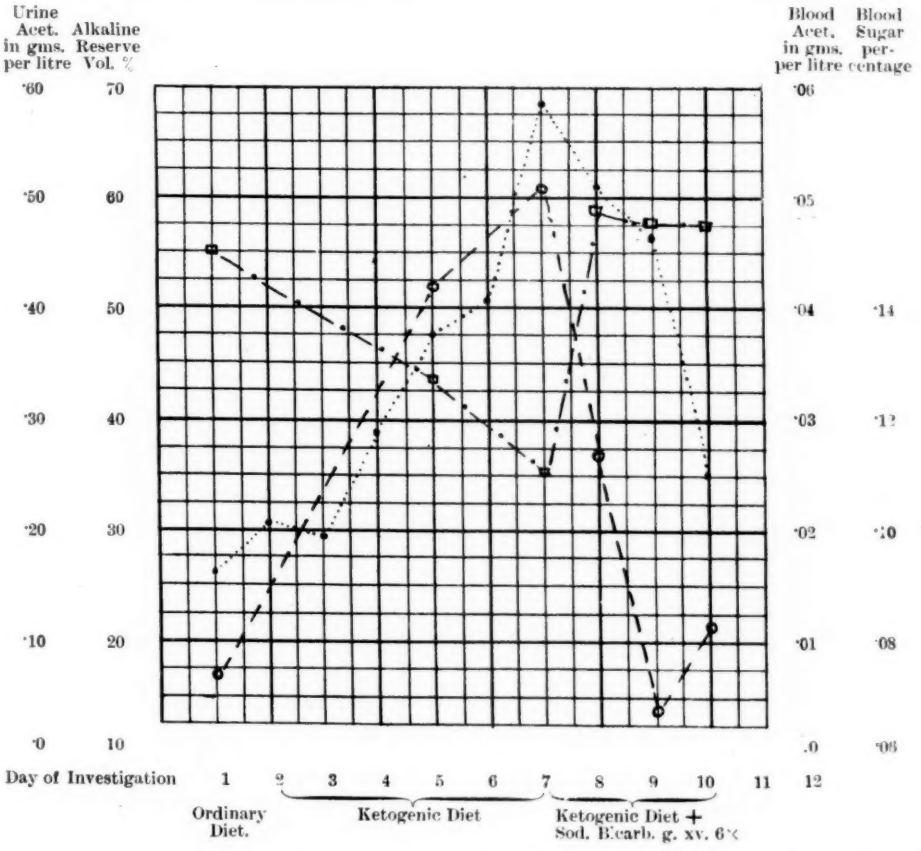


Chart I.

Case No. 3.—Ketogenic Diet followed by Sod. Bicarbonate.



30 to 40 times their usual amount of ketone bodies without any attempt on the part of the body to increase the output or to reduce the urinary percentage by diuresis. The intake of water in these experiments was in

no way limited yet the daily output of urine showed remarkably little variation, considering the marked changes which were apparent in the acetone figures. That acetone differs from other acids in this respect might be explained by its volatility, which renders it capable of excretion by the lungs as well as by the kidneys. No attempt has been made to measure the acetone excretion by the lungs in the present series of cases; but a smell of acetone was perceptible in the breath of only three of our 14 cases, and in these (Nos. 2, 8, and 11), the rise in the acetone of the blood and urine was not as marked as some of the others. The presence of an acetone smell in the breath does not therefore appear to be a reliable criterion of the severity of a ketonæmia.

(ii) *Alkaline Reserve.*

It is strikingly evident from Tables III. to VI. and the charts appended that increase in the acetone bodies of the blood is invariably accompanied by a fall in the alkaline reserve. The nature and degree of the fall was so constant that we were able with some accuracy to predict the behaviour of the plasma-bicarbonate curves in a child who was given a ketogenic diet. A rise in the blood acetone is invariably accompanied by a corresponding fall in the alkaline reserve.

Gamble[24] has demonstrated a similar fall in the serum bicarbonate in fasting children and believes the reduction to be directly and wholly due to an increase in the ketone acids. Talbot, Shaw and Moriarty[25] give further confirmation of this fall in available alkali with a corresponding rise in acetone production during fasting, and it is only to be expected that a similar result would be obtained by the administration of a ketogenic diet. The degree of reduction in the bicarbonate reserve in the various cases is relatively constant. The range of normal variation in the children under investigation was 55 to 69 vol. per cent., while during the ketogenic period the figures varied between 32·3 and 46·8 vol. per cent. The reduction to these values appeared to occur irrespective of the degree of increase in the acetone content of the blood. It would therefore be incorrect to take any individual reading of the bicarbonate reserve as an indication at that time of the possible level of the blood acetone; but it may be assumed that, where the conditions are favourable for the production of ketone bodies, any reduction in the alkaline reserve indicates a definite increase in the blood acetone.

The point next to be considered is whether the fall in the alkaline reserve under these conditions is to be taken as indicating a change in the acidity of the body fluids. In other words, does reduction in alkaline reserve in ketonæmia mean reduced serum pH and consequent acidosis? In this connection we were struck by the invariable fact that patients were to all appearance quite unaffected by the changes which were undoubtedly taking place in their metabolism. As already stated only three of the cases developed a perceptible smell of acetone in the breath, and in no case was increased rate or depth of respiration clinically evident.

A fall in the alkaline reserve such as that obtained above should theoretically result in a change in the acidity of the body fluid, since the rapid washing out of CO_2 *via* the lungs by over-ventilation, which would have been necessary to compensate for the reduction in alkali, did not occur. Gamble[24] has recently pointed out that, until now, we have been inclined to think that little actual increase in plasma acidity takes place even in the presence of greatly reduced bicarbonate. Direct measurement of plasma pH by Cullen's[39] method, however, has shown (*vide* Talbot, Shaw and Moriarty[25]) that even moderate reduction of bicarbonate may cause a considerable fall in pH. It therefore seems justifiable to assume that, in the absence of a definite increase in CO_2 output by over-ventilation, a reduction in the alkaline reserve must be taken as an indication of a reduction in the serum pH, and consequent acidosis. If we apply this assumption to our own results we must conclude that acidosis (or ketosis in our use of the word) may occur in childhood without giving rise to any clinical manifestation of its presence.

(iii) *Blood Sugar.*

Much work on the value of blood-sugar estimations in acidosis and ketosis has already been done but the results so far available seem contradictory. The earlier workers, *e.g.*, Allen[26], state definitely that no fall in the blood sugar takes place even after prolonged fasting. During the past few years, however, this has been contradicted, especially by the American workers, who found a very definite fall in the blood sugar of fasting children. It might be expected that in fasting, where the carbohydrate insufficiency is extreme, a low blood sugar would inevitably follow depletion of the glycogen reserves of the body, but a review of the literature reveals no reference to a low blood sugar after fasting in adults. This does not necessarily mean that such will not occur in children. In them there may be perhaps a more rapid utilisation of the mobilised glucose than in the adult, which would account for the rapid fall in the blood sugar which has been obtained by some of those who have studied fasting children.

Mogwitsch[27] in 1914, recorded a lowering of the blood sugar in five fasting children. In one infant, after a fast of 72 hours, he found that the blood sugar, which was ·09% three hours after the last feed, had fallen to ·047%. Sawyer[28], who gave diets of very low caloric value to several children with very variable results, observed in some cases a slight rise in the blood sugar and in one case a very marked fall to ·020%, a figure which is hardly compatible with life. Talbot, Shaw and Moriarty[25], in eight cases in which they produced a ketosis by fasting, found a marked fall in the blood sugar in all; in some instances figures of ·045% and ·038% were recorded, but in only one of the cases were there any symptoms of hypoglycæmia. Ross and Joseph[29] found a very low blood sugar in one case subject to attacks of cyclical vomiting. As the examination was made between the attacks the lowering noted apparently was not due to vomiting, which we know can give rise to a moderate reduction in the blood sugar values. After a fast of six hours in this case there occurred a fall in the blood sugar from ·100% to ·086%, while 14 hours later it had reached the low level of ·049%. In a series of controls, Ross and Joseph[29] obtained only a very slight fall in the blood sugar on the fourth to the fifth day of starvation.

Schlossmann[30] found that the blood sugar remained normal till 72 hours after food and then fell sharply. Hoeffel and Moriarty[31] fasted two cases of epilepsy eight and nine days respectively, and got a marked fall in the blood sugar in both. In the former a fall of from 0·075% to ·059% was obtained, while in the latter the fall was more marked, from ·100% before the fast to ·052% after nine days' fasting. Shaw and Moriarty[32] kept five epileptic children on a fixed diet for three to four days, after which they were fasted for ten to 14 days, only water being given during the period. A fall in the blood sugar coincident with a fall in the alkaline reserve resulted, but towards the end of the fast both the blood sugar and the alkaline reserve tended to rise again. In all of these cases quoted the fall in the blood sugar took place along with the development of a ketonæmia. Where an excess formation of ketone bodies has been produced by the giving of a ketogenic diet, however, this fall in the blood sugar has not been so marked.

Ross and Joseph[29], in two children on a high fat and low carbohydrate diet, found a slight fall in the blood sugar coinciding with the increase in the fat-carbohydrate ratio. In the first case the normal fasting blood sugar was ·096% and after ten days on a ketogenic diet had fallen to ·084%, while in the second case it fell from ·112% to ·091%

In the ketosis accompanying infections a high fasting blood sugar has been noted by Tallerman[33], while Chapin and Myers[34] found a slight fall in the blood sugar in cases of acidosis (not necessarily ketosis) accompanying gastro-enteritis and malnutrition.

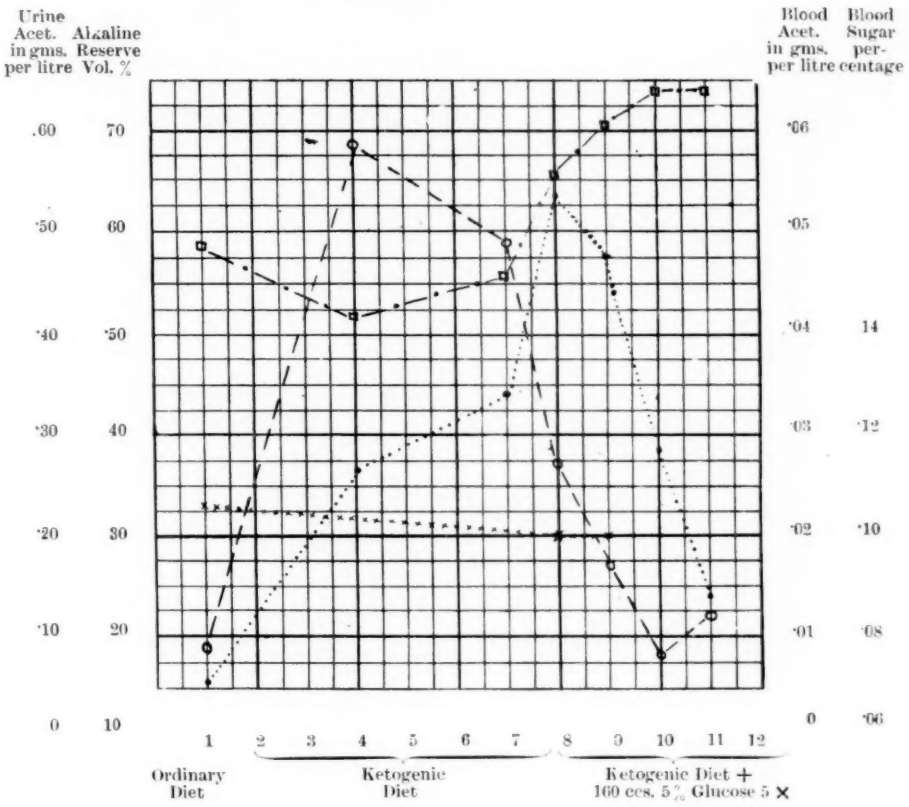
Langfeldt[35] in the case of adults, by administering acid either *per os* or intravenously and thus causing an acidosis, states that glycogenolysis takes place followed by hyperglycæmia and glycosuria, and Haldane[36] found that though a disturbance of carbohydrate tolerance may result from acidosis, the fasting blood sugar is usually normal. He concluded that acidosis leads to a disturbance of carbohydrate storing and not to a disturbance of its oxidation.

The fasting blood sugar was examined in some of our cases at the beginning of the experiment and also after ketogenic periods of varying duration; as is shown in Tables III to VI and Charts I to IV, no appreciable fall in the blood sugar was obtained. The most marked fall was in Case No. 6, where the normal fasting blood sugar was ·106% and after eight days on a ketogenic diet had fallen to ·085% and four days later was still at the same level. The absence of any marked alteration in the blood sugar values in this series of cases is difficult to correlate with the theory that excess of ketone acids is the result of relative carbohydrate insufficiency. The type of glucose circulating in the blood was, however, not investigated, and it is recognised that this may be a point of considerable importance, since it is known that all types of glucose are not equally efficient as antiketogenics. The maintenance of a normal blood sugar content can be explained on the assumption that the shift in acid-base balance to the acid side, resulting from the ketonæmia, inhibits the storing of any carbohydrate, and so provides that all the available supply is used to maintain a normal blood sugar. As already stated Haldane[36] showed that the production of an acidosis results in a disturbance of the body's capacity to store glucose but not to oxidise it. It therefore seems possible that the accumulation of ketone acids to excess may in itself tend to keep the blood sugar normal by diminishing the amount stored. It is even conceivable that, so long as

storing does not take place, sufficient glucose is available from other sources, such as protein, to maintain the level of the blood sugar even during the administration of an almost entirely carbohydrate-free diet. Further work on the behaviour of the carbohydrate metabolism during ketonæmia is necessary and is at present under consideration.

CHART II.

Case No. 8.—Ketogenic Diet followed by Glucose.



III.—DISAPPEARANCE OF KETONÆMIA AND KETONURIA UNDER VARIOUS FORMS OF TREATMENT.

In order to test the effect of various changes in diet on the ketonæmia and ketonuria the following further studies in the same series of cases were made, when as a result of the ketogenic diet a definite rise in the blood acetone and fall in the alkaline reserve were apparent:—

(*a*) Five children (Cases Nos. 1-5) were kept on the ketone-producing diet, with in addition the administration of sodium bicarbonate.

(*b*) Four children (Cases Nos. 6-9) were kept on the ketogenic diet with the addition of glucose.

(*c*) Four children (Cases Nos. 10-13) were changed from a ketogenic diet to the ordinary diet for children of the same age.

(*d*) One child (Case No. 14) was kept on the ketogenic diet with the addition of both glucose and sodium bicarbonate.

The effects of these various changes are shown graphically in Charts I to IV.

A comparison of the results obtained in the four groups is interesting. The addition of glucose to the ketogenic diet and the change to the ordinary diet are, as one would expect, similar in their effect. Patients subjected to either of these forms of procedure showed a rapid diminution in the ketonæmia and the ketonuria with a coincident rise in the bicarbonate content of the serum, all three values returning to normal within four days of the commencement of treatment. In no case did recovery result in markedly increased excretion of ketone acid, as the blood and urine acetone fell simultaneously. It was therefore obvious that the effect of the administration of glucose or of an ordinary diet was to arrest the formation of acetone bodies, with a consequent rapid diminution in the amounts retained and excreted.

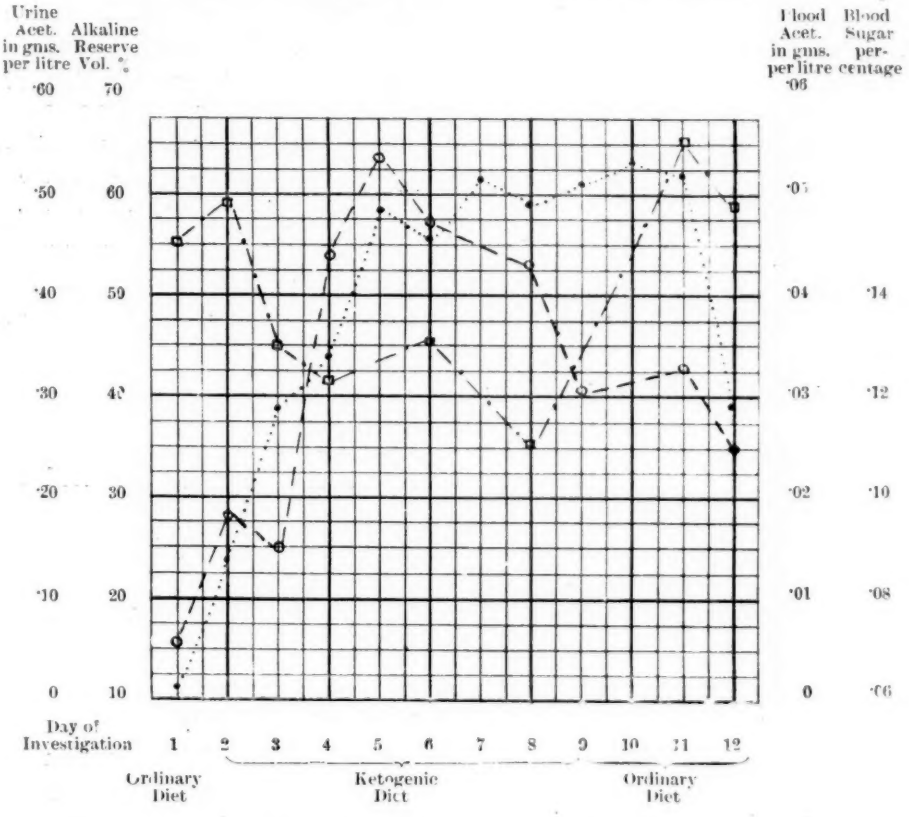
A further point of interest is that the amount of glucose administered was smaller than that generally recommended to keep the fat-glucose ratio within the antiketogenic border line. The ratio of ketogenic to antiketogenic units in the acid-producing diet was, as calculated from Shaffer's[2] data, roughly 3·5 to 1. The addition of 30 grms. of pure glucose *per diem* reduced the ratio to 2 to 1. In spite of the fact that a ratio of 1 to 1 should be necessary for the prevention of ketogenesis the 2 to 1 ratio seemed to be adequate for the reduction of the ketonæmia present in our cases. Whether this was due to the fact that by the time glucose was supplied the body had already attempted adjustment of the metabolism by the conversion of protein into carbohydrate, is not clear as nitrogen output was not estimated, but the results raise a point of considerable importance in the study of ketogenesis.

The addition to the ketogenic diet of sodium bicarbonate in doses of 120 to 180 grains *per diem* gave less uniform results. While two of the cases appeared to return to normal within four days and were not followed further, each of the remaining cases showed some anomaly which we were at a loss to explain. Case 1, for example, whose blood acetone showed unusually little change throughout the whole course of the experiment, presented a distinct rise in the acetone output immediately after the administration of sodium bicarbonate, while at the end of the experiment the ketone percentages in blood and urine were still higher than they had been on a general diet. One other case responded by a steady gradual reduction in the urinary ketone, but with a steady rise in the blood acetone. The only consistent result obtained by the administration of alkali was a return of the bicarbonate reserve to normal or slightly high values. From a

consideration of the factors influencing the production of excess of ketone acids in the body it could hardly be expected that sodium bicarbonate would have as favourable an effect on the ketonæmia as glucose. Nevertheless it seemed possible that the alkali might assist the rapid elimination of ketone acids already produced and so give rise to increased acetone output in the urine and a possible diminution in the degree of ketonæmia. This however proved not to be the case for, where a favourable result was obtained, the urinary values fell along with the blood values.

CHART III.

Case No 11.—Ketogenic Diet followed by Ordinary Diet.



Recent investigations by Haldane[36] and by Shaffer[2] have shown that changes in the acid-base balance may exert a profound influence on the carbohydrate metabolism. Support for this view has been provided by Ellis[37] and by Haldane[35], both of whom noted that acetone bodies appear in the urine in alkalæmia and after the consumption of very large doses of sodium bicarbonate. One of us (G. G.) in a former investigation of tetany[38] attempted to produce alkalæmia in normal children by the administration of bicarbonate but found that this was merely excreted, and that the alkaline reserve of the plasma remained normal. In order to make

a further test of the administration of alkali on acetone production, sodium bicarbonate, in doses of from 180 to 600 grains in the 24 hours, was given to two children aged 9 and 10 years. According to the formula of Cullen and Austin[39] $\frac{38g}{W}\left(\frac{38 \text{ grms. Sod. Bicarb.}}{\text{Weight of Child.}}\right)$ 600 grains daily is ample to produce a marked increase in the plasma bicarbonate. This it entirely failed to do in spite of the fact that one of the subjects for the experiment was a chronic nephritic, whose renal efficiency might have been expected to interfere with alkali excretion. In neither case did acetone appear in the urine up till the fifth day after the administration of the last dose of bicarbonate.

In view of the fact that, as recently stated by Shaffer[2], alkali is essential for the complete oxidation of glucose by air or H_2O_2 in vitro, one would expect a quicker return of the blood acetone to normal if glucose and sodium bicarbonate were administered together. In one case where a ketogenic diet had been administered, the effect of this combination of glucose and alkali was tested. It was found, however, that the alkali had no apparent effect, the blood acetone and the urine acetone acting in the same way as when glucose alone was administered. The effect of glucose is therefore to arrest the formation of ketone bodies and so permit of their removal within a few days. The effect of alkali administration on the blood and urine was not constant and could therefore not be depended on, except to produce a rapid return of the alkaline reserve to a normal or even slightly raised figure.

IV.—CONCLUSIONS.

(1) Ketonuria occurred in 54·7% of 300 consecutive cases admitted to the Royal Hospital for Sick Children, Glasgow.

(2) The Van Slyke method gives normal blood acetone values of from 0 to 0·017 grms. per litre in children of 6 to 12 years of age.

(3) An increase in the blood acetone from 2 to 40 times its normal amount occurs on the administration of a ketogenic diet. This rise is accompanied by a fall in the alkaline reserve and an increase in the urinary acetone, but there is no definite reduction in the blood sugar.

(4) In ketonæmia, glucose administration results in rapid diminution of blood and urine acetone, with a corresponding rise in the alkaline reserve.

(5) In ketonæmia the administration of sodium bicarbonate cannot be depended on to reduce the blood and urine acetone, but is beneficial in procuring a rapid return to normal of the low alkaline reserve.

(6) Glucose administration would therefore seem the rational and correct treatment for ketonæmia or ketosis, but sodium bicarbonate would appear to be of use in the immediate relief of any symptoms which may be due to the reduction in the body alkali.

The expenses of this investigation have been defrayed by the Medical Research Council to which we desire to express our gratitude.

TABLE III.

CASES ON KETOGENIC DIET TREATED WITH BICARBONATE OF SODA.

Case No	Days of Investigation.	Diet and Treatment.	Acetone in Urine in grms. per litre.	Acetone in Blood in grms. per litre.	Alkaline Reserve. Vol. per cent.	Percentage of Blood Sugar.
1.	1	Ordinary Diet	...	·015	61·3	·086
	2	Ketogenic Diet	·188	...	...	...
	3	,, ,, ...	·345	...	...	...
	4	,, ,, ...	·512	...	...	...
	5	,, ,, ...	...	·024	...	·080
	6	,, ,, ...	...	·312	...	...
	7	,, ,, ...	...	·022	46·8	...
	8	Ketogenic Diet + Sod. Bic. gr. xx 4 times ...	·669	...	52·6	·080
	9	,, ,, ,, ,, ...	·578	...	...	...
	10	Ketogenic Diet + Sod. Bic. gr. xl 4 times ...	·379	·029	46·8	...
	11	,, ,, ,, ,, ...	·644	...	59·4	...
2.	1	Ordinary Diet	...	·017	57·4	·098
	3	Ketogenic Diet	·189	...	...	...
	4	,, ,, ...	·536	...	..	...
	5	,, ,, ...	·719	·061	32·3	·086
	6	,, ,, ...	·724	...	...	...
	7	,, ,, ...	·756	·063	52·6	...
	8	Ketogenic Diet + Sod. Bic. gr. xxx, 6 times ...	·784	...	...	...
	9	,, ,, ,, ...	·668	·029	58	...
	11	,, ,, ,, ...	·544	·009	71·9	...
3.	1	Ordinary Diet	·165	·007	55·5	...
	2	Ketogenic Diet	·204	...	...	...
	3	,, ,, ...	·194	...	...	...
	4	,, ,, ...	·286	...	...	...
	5	,, ,, ...	·378	·042	43·9	...
	6	,, ,, ...	·406	...	...	...
	7	,, ,, ...	·586	·051	36·1	...
	8	Ketogenic Diet + Sod. Bic. gr. xx, 6 times ...	·516	·027	59·4	...
	9	,, ,, ,, ...	·472	·004	67·1	...
	10	,, ,, ,, ...	·254	·012	57·6	...
4	1	Ordinary Diet	...	·006	62·3	...
	3	Ketogenic Diet	·174	...	...	...
	4	,, ,, ...	·253	...	...	...
	5	,, ,, ...	·372	...	...	...
	6	,, ,, ...	·266	...	...	...
	7	,, ,, ...	·454	·059	38·1	...
	8	Ketogenic Diet + Sod. Bic. gr. xxx, 5 times ...	·359	...	...	...
	9	,, ,, ,, ...	·221	·079	62·3	...
	10	,, ,, ,, ...	·110	.	...	...
	11	,, ,, ,, ...	·093	·126	52·6	...
5.	1	Ordinary Diet	...	·010	42·9	·098
	2	Ketogenic Diet	·018	...	...	...
	3	,, ,, ...	·056	...	...	...
	4	,, ,, ...	·154	...	...	...
	5	,, ,, ...	·071	...	...	...
	6	Ketogenic Diet + Sod. Bic. gr. xxx, 4 times ...	·253	·080	42·9	·088
	7	,, ,, ,, ...	...	...	...	·094
	8	,, ,, ,, ...	·345	...	57·4	...
	9	,, ,, ,, ...	·342	...	...	...
	10	Ordinary Diet	·243	·015	68	·100
	11	,, ,, ...	·195	...	...	...

TABLE IV.

Cases on Ketogenic Diet Treated with Glucose.

Case No.	Days of Investigation.	Diet and Treatment.	Acetone in Urine in grms. per litre.	Acetone in Blood in grs. per litre.	Alkaline Reserve. Vol. per cent.	Percentage of Blood Sugar.
6.	1	Ordinary Diet	...	·004	69	...
	2	Ketogenic Diet	·012	...	69	·106
	3	,, ,, ...	·136	...	...	...
	4	,, ,, ...	·074	...	...	...
	5	,, ,, ...	·166	...	..	...
	6	,, ,, ...	·359	...	...	...
	7	,, ,, ...	·645	·032	41	·094
	8	,, ,, ...	·553	...	...	...
	9	,, ,, ...	·386	·087	53·6	·085
	11	,, ,, ...	·248	·011	60-70	·084
	14	Ketogenic Diet + 100 cc. 5 % Glucose 5 times ...	·823	·084	38	...
	15	,, ,, ,, ..	·818	·042	38	...
	16	,, ,, ,, ...	·513	·065	40	...
	17	,, ,, ,, ..	·595	·051	42·9	·100
7.	1	Ordinary Diet	...	·001	49·7	·094
	3	Ketogenic Diet	·048	...	...	...
	4	,, ,, ...	·343	...	...	...
	5	,, ,, ...	·696	...	...	...
	7	,, ,, ...	1·255	·041	42·9	·098
	8	Ketogenic Diet + 100 cc. 5 % Glucose 6 times ...	·541	...	...	...
	9	,, ,, ,, ...	·581	·003	59·4	...
	10	,, ,, ,, ...	·304	...	...	...
	11	,, ,, ,, ...	356	·019	57·4	...
	14	,, ,, ,, ...	·043	...	...	...
8.	1	Ordinary Diet	·054	·009	59·4	·106
	4	Ketogenic Diet	·254	·058	42·6	...
	7	,, ,, ...	·347	·049	46·8	...
	8	Ketogenic Diet + 100 cc. 5 % Glucose 5 times ...	·532	·027	56·5	·100
	9	,, ,, ,, ...	·478	·017	61·4	·100
	10	,, ,, ,, ...	·284	·008	64·2	...
	11	,, ,, ,, ...	·148	·012	64·2	...
9.	1	Ordinary Diet	...	·016	61·3	·100
	3	Ketogenic Diet	·048	...	...	...
	4	,, ,, ...	·576	...	...	...
	5	,, ,, ...	1·016	...	...	...
	6	,, ,, ...	·377	...	...	...
	7	,, ,, ...	·359	·155	41	·094
	8	Ketogenic Diet + 100 cc. 5 % Glucose 6 times ...	·238	...	...	...
	9	,, ,, ,, ...	·130	·003	53·6	...
	10	,, ,, ,, ...	·083	...	...	...
	11	,, ,, ,, ...	·051	·034	56·4	...
	12	,, ,, ,, ...	·058	...	...	...

TABLE V.

CASES ON KETOGENIC DIET TREATED WITH ORDINARY DIET.

Case No.	Days of Investigation.	Diet and Treatment.	Acetone in Urine in grms. per litre.	Acetone in Blood in grms. per litre.	Alkaline Reserve. Vol. per cent.	Percentage of Blood Sugar.
10.	1	Ordinary Diet	·170	·012	65·2	·100
	2	Ketogenic Diet	·098	...	...	...
	3	,, ,, ...	·295	·085	44·6	·102
	4	,, ,, ...	·389	·088	39·1	·098
	5	,, ,, ...	·570	·084	40	·098
	6	,, ,, ...	·440	...	...	...
	7	Ordinary Diet	·256	·054	...	...
	8	,, ,, ...	·106	...	...	...
	9	,, ,, ...	·125	·0078	69	·106
11.	1	,, ,, ...	·019	·0064	55·5	·098
	2	Ketogenic Diet	·148	·018	59·4	...
	3	,, ,, ...	·298	015	45·6	...
	4	,, ,, ...	·346	044	42	...
	5	,, ,, ...	·489	·054	...	...
	7	,, ,, ...	·456	·047	46·5	...
	8	,, ,, ...	·523	...	...	...
	9	,, ,, ...	·498	·043	36·1	...
	10	Ordinary Diet	·518	·031	...	...
	11	,, ,, ...	·527	...	...	...
	12	,, ,, ...	·524	·033	65·2	...
	16	,, ,, ...	·298	·025	59·2	...
	17	,, ,, ...	·198	...	...	..
12.	2	Ketogenic Diet	272	...	...	...
	3	,, ,, ...	·372	...	...	...
	4	,, ,, ...	·346	..	...	·090
	5	,, ,, ...	·412	...	...	...
	6	,, ,, ...	·416	·051	45·8	...
	7	Ordinary Diet	·541	·034	48·7	...
	8	,, ,, ...	·382	·009	62·5	·100
	9	,, ,, ...	·339	...	...	...
	10	,, ,, ...	·192	·012	64·2	...
	11	,, ,, ...	·204	...	...	...
13.	1	,, ,, ...	·098	·064	62	..
	6	Starvation Diet	·409	·037	40	·090
	7	,, ,, ...	·553	...	...	·086
	8	,, ,, ...	·434	...	..	·086
	9	,, ,, ...	·540	·045	40	·094
	10	Ordinary Diet	·267	...	...	...
	11	,, ,, ...	·277	...	...	...
	12	,, ,, ...	·099	·009	64·2	·099
	13	,, ,, ...	·122	...	...	·096

TABLE VI.

CASES ON KETOGENIC DIET TREATED WITH GLUCOSE AND BICARBONATE OF SODA.

Case No.	Days of Investigation.	Diet and Treatment.	Acetone in Urine in grms. per litre.	Acetone in Blood in grms. per litre.	Alkaline Reserve. Vol. per cent.	Percentage of Blood Sugar.
14.	1	Ketogenic Diet	...	...	...	...
	2	,, ,, ...	·149	...	...	·106
	3	,, ,, ...	·325	...	...	...
	6	,, ,, ...	·488	·042	58	...
	7	Ketogenic Diet + Sod. Bic. gr. xxx, 100cc. 5 % Glucose 5 times	·512	·038	55·5	·100
	8	,, ,, ,, ...	·453	·012	...	...
	9	,, ,, ,, ...	·209	...	...	...
	10	,, ,, ,, ..	·126	...	...	...

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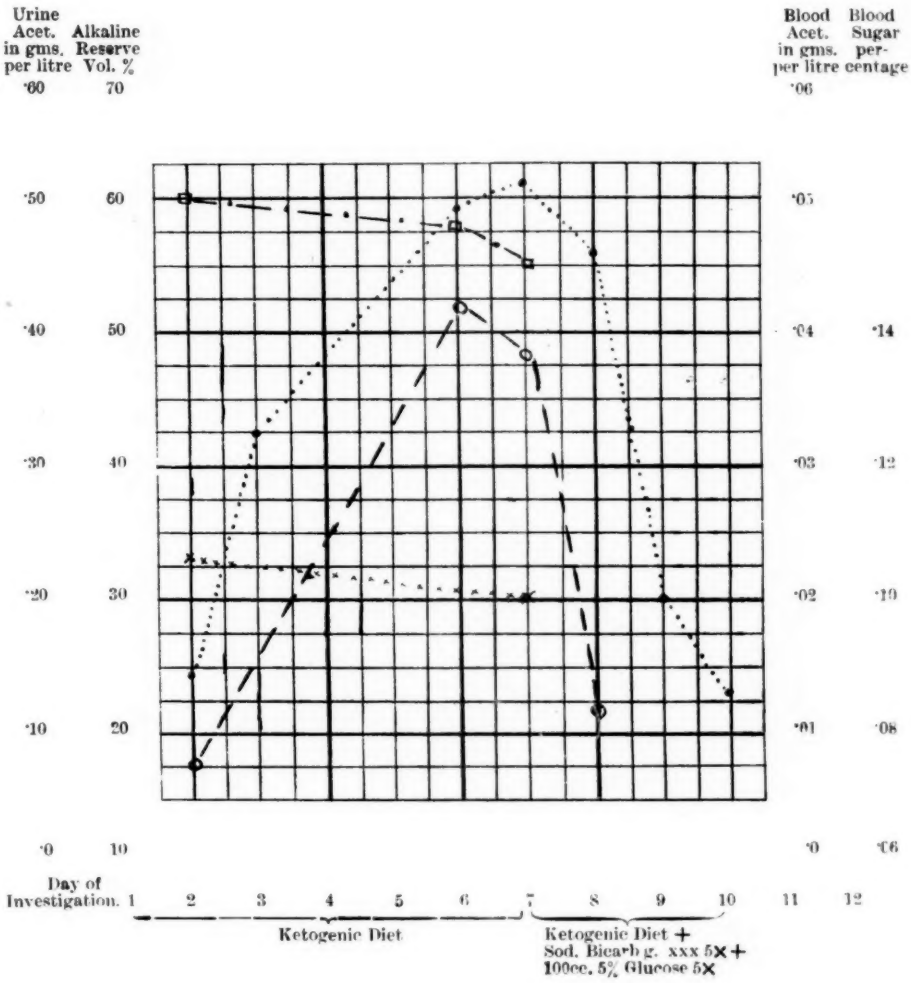
Chart IV.

Case No. 14.—Ketogenic Diet followed by Glucose and Sod. Bicarbonate.



Erratum in August issue.

It is regretted that by an oversight in correction the Table on p. 231 of the August issue was printed with obvious errors. It should read as follows:—

I.Q.	25 or under.	25 to 50	50+	60+	70+	80+	90+	100+	Total Cases.	
Dull or backward or both...	—	—	10	52	112	76	25	18	293	
Physically defective ...	—	—	3	12	17	7	3	2	44	
	—	—	13	64	129	83	28	20	—	337
Feeble-minded	—	48	140	208	117	7	—	—	—	520
Imbecile or idiot	10	87	36	6	4	—	—	—	—	143
	—	—	–	—	—	—	—	—	—	1,000

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SCIENTIFIC ACTIVITIES OF THE BRITISH MEDICAL ASSOCIATION.

The activities of the British Medical Association are not less wide than the interests of the medical profession. One of these interests is certainly the increase and diffusion of knowledge which will open to the practitioner a wider field of efficiency and of service. In such an enterprise the Association has always taken, and will continue to take, an active part.

The "British Medical Journal."

In the *Journal* the Association possesses an agency of the highest value for every earnest student of his or her profession. Contributions of recognised scientific and practical merit are received from experts in all departments of professional activity, and clinical notes on diagnosis and treatment form a feature of every issue. Here, too, are to be found the records of the various professional societies, notices of new books, and an account of modern developments in medicine, surgery and pharmacy. Altogether, the *British Medical Journal* occupies a leading place in the medical journalism of the British Empire, and no practitioner who reads the *Journal* with reasonable care can fail to keep abreast of current knowledge in all the fields of medicine and surgery in this country on both their clinical and their laboratory sides, or to be in touch with thought abroad on the same subjects.

Other Publications of the Association.

"*Journal of Neurology and Psychopathology.*" In no department of medicine has the impetus to renewed study and fresh research supplied by the problems of the war and post-war periods been more strikingly manifest than in that of nervous and mental disease. As compared with that of Continental countries and of America, English medical journalism has been slow to deal in adequate fashion with the progress of the last decennium towards better understanding of nervous and mental mechanisms. This gap has largely been filled by the *Journal of Neurology and Psychopathology* which is devoted to the furtherance of knowledge along modern lines in all that pertains to the nervous system, and is now published by the Association. The Editor-in-Chief is Dr. S. A. Kinnier Wilson.

"*Periodicals of Medicine and Allied Sciences in British Libraries,*" by Prof. R. T. Leiper, M.D., D.Sc., F.R.S. The object of this book is to indicate where much of the periodical literature of medicine and the allied sciences may be consulted, in Cambridge, Edinburgh, Glasgow, Liverpool, London, Manchester and Oxford.

Annual Scientific Meetings of Association.

At the Annual Scientific Meetings of the Association which are held in July in a different district each year, matters relating to the clinical and scientific aspect of professional work are discussed. The Sections are open free to all members, and are attended by many members and foreign guests eminent in the various subjects. Many social meetings and entertainments, civic and other, are held in connection with the Annual Meetings. Ladies are welcomed at these meetings and functions, and attend in great numbers. The next Annual Meeting will be held at Edinburgh in July, 1927.

ACUTE INVAGINATION OF THE INTESTINE IN SMALL CHILDREN.

BY

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In 1905, in the "Mitt. aus Grenzgebiet der Medic. u. Chir.," Hirschsprung recorded 107 cases of acute intestinal invagination observed by him in the course of 34 years (1871-1904). In referring to this paper, I shall only quote the treatment and its results. Seventy-three children were treated entirely by non-surgical means; 59 of these were cured and 14 died In 11 children an attempt at reduction was first tried and afterwards laparotomy was resorted to; of these three were cured and eight died. This gives a total of 84 cases, 62 of which were cured and 22 died, which corresponds to a mortality of 26·2%. Sixteen children were operated on in the first instance; three of these were cured and 13 died.

Seven children were not treated, either because they were moribund on admission or because the invagination was only recognised at the autopsy.

During the 20 years (1906-1925) in which I have been in charge of the Dronning Louise's Children's Hospital I have had altogether 115 cases of acute intestinal invagination, or 5·75 cases on an average per annum. I will now give an account of these cases.

TABLE I.

Age of the Children (115 *cases*).

0– 3 months	1 case.	Under 1 year	73 cases.
4– 6 ,, ...	21 cases.	1–2 years	23 ,,
7– 9 ,, ...	34 ,,	2–3 ,, ...	15 ,,
10–12 ,, ...	17 ,,	3–4 ,, ...	4 ,,
		Over 4 ,, ...	0 ,,

It will be seen from the above that I only had one case during the first three months of life, while in the third three months I encountered 34 cases or nearly one-third of the total number. Whether this has any connection with the fact that the seventh-ninth month is the period when weaning usually takes place I cannot say. As will be observed from the table, I had 73 children under 1 year of age, while none of them were over 4.

TABLE II.

Sex of the Children (107 *cases*).

Boys	72 cases.	Girls	35 cases.

The reason that only 107 children are recorded here, although I had 115 cases, is that five children got invagination twice and one child no less than four times,

As the table shows there were twice as many boys as girls. This marked difference in sex, which is also found in most sets of statistics, has given rise to various ætiological theories (retention of the testis, phimosis, etc.) to which I do not believe any value whatever can be attributed. I shall, therefore, merely recall that such different diseases as congenital pyloric stenosis and infantile tetany exhibit exactly the same sex distinction.

Of the 107 children, 50, or about half, were the only children in the family, a phenomenon which is found in many other series of statistics and which cannot be explained.

Of the 73 infants under 1 year of age, 26 were entirely breast-fed and 40 received *allaitement mixte*, while only seven were bottle-fed. This fact is interesting because it shows that artificial feeding does not predispose to invagination.

Of the 107 children, no less than 74 were absolutely healthy at the time when the invagination occurred; 15 had antecedent diarrhœa and 11 were said to be inclined to be constipated. In seven of the children the information was doubtful.

It will thus be seen that acute invagination of the intestine in particular attacks healthy breast-fed children and those having *allaitement mixte*. Whether this depends upon breast-fed children having weaker antiperistalsis than bottle-fed ones I am unable to say. Further, it is observed that the disease has a special predilection for solitary children.

According to the available evidence, acute invagination of the intestine seems to be commoner in the Anglo-American countries and in Denmark than in many other lands, such as, for example. France, Germany, Norway and Sweden. Although it has been maintained that this difference in frequency is due to the abuse of purgatives in the first-named countries, I can vouch for the fact that at any rate in the case of Denmark such a contention is quite without foundation. On going through the clinical histories of my cases I have found that only a very few of the children received purgatives immediately preceding the occurrence of the invagination.

In the present article, however, I shall not enter further into the different ætiological and pathogenetic theories which have seen the light of day, but I will pass on to discuss the different forms of intussusception which my material embraces.

Forms of Intussusception.

Only *acute descending* invaginations are being dealt with here. Chronic invaginations in my experience are extremely rare in small children; and as regards ascending invaginations they are certainly not rare, but they practically all come on in agony and are therefore unimportant clinically.

There are many different forms of acute descending invaginations, but unfortunately the various authors do not regard them in the same light, in fact they even give different names to the same forms. This want of uniformity in the point of view and nomenclature unhappily makes it quite impossible to draw reliable conclusions from the different series of statistics.

My own standpoint is as follows: I divide invaginations into two main groups—large intestine and small intestine invaginations. Each of these main groups are again divided into two sub-groups:—

I.—*Large intestine invaginations* are either purely *colic*. that is to say where a variable portion of the colon is invaginated in a lower part of the colon, or *ileo-cæcal, i.e.,* where the head of the invagination is formed by the cœcum or ileo-cœcal valve. In the latter variety the vermiform appendix is thus situated in the intussuscipiens.

II.—*Small intestine invaginations* are either purely *iliac*, that is to say where a piece of small intestine is invaginated in a piece of small intestine below it, or *ileo-colic* by which is understood a small intestine invagination, situated low down, which goes through the ileo-cœcal valve and is found in the ascending colon or sometimes goes further down into the colon. In the latter form, therefore, the cœcum and appendix are external to the invagination in contrast to the ileo-cœcal invagination.

Besides these principal forms there are *mixed forms* and *double forms*, but as these are quite exceptional in my material I will not deal further with them.

My material contains the following forms:—

TABLE III.

Large intestine invaginations	...	...	**Total**	**87**	**cases**	**(75·7%).**
Ileo-cœcal	,,	...	...	...	**66**	,,	**(57·4%).**
Colic	,,	...	...	...	**21**	,,	**(18·3%).**
Small intestine invaginations	...	...	**Total**	**25**	**cases**	**(21·7%).**
Ileo-colic	,,	...	...	...	**19**	,,	**(16·5%).**
Iliac	,,	...	...	...	**6**	,,	**(5·2%).**

In addition to these there were three mixed forms, namely, two iliac-ileocœcal invaginations and one iliac-ileocolic.

It will thus be observed that three-quarters of all my intussusceptions are of the large intestine and only one-quarter involve the small intestine. Further, over a half of all the cases are ileo-cœcal invaginations, a fact which, moreover, is found in almost all statistics.

It is of great interest to see how the various forms differ with respect to the age of the children. Out of 87 large intestine invaginations no less than 59 occurred in infants under 1 year old, and only 28 in children over 1 year old. But out of the 25 small intestine invaginations only 11 occurred in children under 1 year old, while there were 14 in children over 1 year old.

Small intestine invaginations are, therefore, relatively rare in the first year of life and increase in frequency with age, but large intestine invaginations are particularly common in the first year, probably on account of the anatomical conditions, for—as is known—infants under 1 year have a high ascending mesocolon and a long, mobile sigmoid flexure.

Clinical Features.

Acute intestinal invagination has four cardinal symptoms: (1) periodic attacks of colic; (2) vomiting; (3) passage of blood and slime per anum; and (4) presence of a tumour in the abdomen.

(1) *Pain* is the most constant and usually also the first symptom, as it is due to tension and dragging on the mesentery and, therefore, it undoubtedly sets in immediately the invagination occurs. It often starts very suddenly and takes the form of peristaltic attacks of colic which may be so violent that the child not only suffers intensely, but sometimes even collapses. On the other hand it is remarkable that in the pain-free intervals the children often do not convey the impression of being seriously ill at all. They lie quietly and have a moist, clean tongue, normal temperature, good pulse and an abdomen which is not distended and in its appearance in no way betrays what is happening in its interior. But it should be noted that the children are almost always remarkably pale and have a characteristic apathetic facial expression which is almost typical of patients with invagination. No wonder therefore that not only the mother, but also the doctor, who is not familiar with the clinical aspect of intussusception, may be puzzled by the peacefulness and apparent comfort displayed by the child in the intervals between the attacks of pain.

(2) The second cardinal symptom is *vomiting* which usually appears shortly after the pain has set in, but sometimes not until five-ten hours afterwards. In rare cases vomiting may be the first symptom and only very exceptionally is it entirely absent. The vomit at first consists of food, and later contains a lot of bile, but is never fæculent when the case is not an old one. I have met with two cases of vomit containing blood, which is stated to be very rare, in both instances in children with ileo-colic invaginations.

Like the pain, vomiting is an extremely constant symptom. Both of them are most severe and more prolonged in small intestine invaginations than in large intestine invaginations, and on the whole it is the rule that small intestine invaginations produce more rapidly appearing fever and greater general disturbance than happens in the case of large intestine invaginations.

(3) The third cardinal symptom is the *passage of blood and slime per anum*. As a rule a natural motion is passed simultaneously with, or shortly after, the pain and vomiting have started, but then intestinal obstruction occurs, for neither fæces nor flatus is passed, but only blood and slime, either spontaneously, or on examination, or with an enema. Usually there is only a small quantity of blood and slime, but sometimes there may be much hæmorrhage and this indicates that probably it is a colic invagination. It is characteristic of the blood and slime that it is not mixed with fæces and possesses no fæcal smell, but has a peculiar insipid odour which is

absolutely typical, in fact almost pathognomonic of invaginations. It is important to remember this because there is another disease in which blood and slime are passed per anum and which is therefore not uncommonly confused with intussusception, namely follicular entero-colitis. But in this disease the blood and slime are mixed with the motions and have a pronounced fæcal smell. Moreover there are, as a rule, both fever and intoxication right from the very onset of the illness, symptoms which never occur in connection with recent intussusception.

The passing of typical blood and slime is pathognomonic of intussusception, but is not by any means constantly found. In my cases the facts were as follows. In all the 21 colic invaginations there was passage of blood and slime. In the 66 ileo-cœcal invaginations this symptom was present in 61 cases, but was absent in five. In the 19 ileo-colic invaginations the passage of blood was absent in only one case, but in five of the six iliac invaginations it did not occur.

From this it will be observed that the presence or absence of this symptom may be a guide in deciding which form of invagination we have to deal with in any given case.

Of greater importance in topical diagnosis however is perhaps the stage of the disease at which the passage of blood starts. On this point my material indicates the following:—

TABLE IV.

	Time when Blood was passed after the Onset of the Invagination.				No Blood Passed.
	Hours.				
	0-6	6-12	12-24	24-48	
21 Colic invaginations	19	1	1	0	0
66 Ileo-cœcal ,,	42	16	3	0	5
6 Iliac ,,	0	1	0	0	5
19 Ileo-colic ,,	5	2	6	5	1

From this it will be seen that in large intestine invaginations the passage of blood occurred immediately or during the first 12 hours of the illness in about 90% of the cases, while in no case did it take place later than the first 24 hours (apart from the five cases where none at all was passed). It was quite different with the ileo-colic invagination, where in over half of the cases blood did not appear until 12-48 hours after the invagination had started. In the iliac invagination no blood was seen as a rule.

(4) The fourth cardinal symptom is *the invagination tumour in the abdomen*. The demonstration of this is often difficult without narcosis, even in cases where a long tumour is present, and one must, therefore, never refrain from diagnosing intussusception because a tumour cannot be detected without an anæsthetic. It is almost always possible to palpate an invagination tumour under an anæsthetic, and amongst my cases I have only six in which I could not detect any tumour. One case was an ileo-colic invagination of 12 hours' standing in a child of 8 months, where the lesion was only recognised at the autopsy. The other five cases were probably colic invaginations; there were attacks of colic, vomiting, the passage of typical blood and slime, and the invaginations were easily reduced by means of injections of water.

I was able to palpate the invagination tumour in 109 cases, and I will now give a brief account of the situation, size and other relations of these tumours in the different forms of invagination.

In the *ileo-cæcal* invagination the commonest finding was a banana-shaped tumour lying to the right of the umbilicus and stretching up towards the right costal margin. I have found a tumour of a size and shape like that shown in Fig. 1 in over half of my cases of ileo-cœcal invaginations. In some cases very long tumours are found which extend right over into the left side of the abdomen (Fig. 2). Sometimes parts of the swelling may

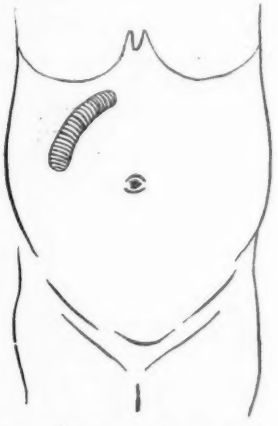

Fig. 1.—Inv. Ileo-cœcal, 29 hours (♀ 7 months)

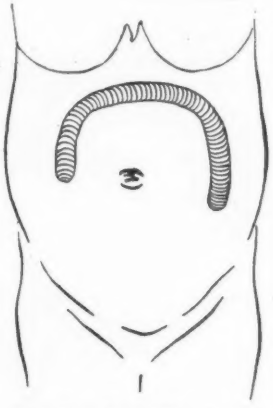

Fig. 2.—Inv. Ileo-cœcal, 9 hours (♀ 3 months)

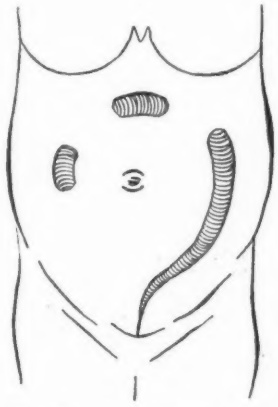

Fig. 3.—Inv. Ileo-cœcal, 20 hours (♀ 7 months)

be hidden, so that one at first thinks there are several separate tumours (Fig. 3), but as soon as one begins to reduce it, it is soon discovered that there is only one tumour. In only eight out of 66 ileo-cœcal invaginations was the tumour palpable in the rectum. It may be added that the length of the tumour is independent of the duration of the illness; the relatively small tumour seen in Fig 1, for instance, was due to an invagination which had lasted for 29 hours, while the long one in Fig. 2 had only existed for nine hours.

In *colic* invaginations the tumour almost always lies to the left of the umbilicus, corresponding with the descending colon, and has an almost vertical course (Fig. 4). Sometimes, however, the tumour is only felt

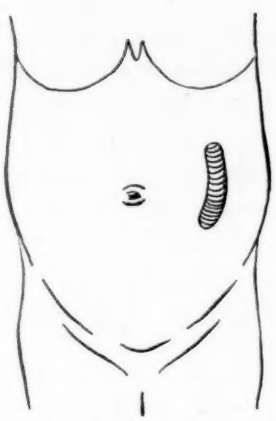

Fig. 4.—Inv. Colic, 32 hours (♂ 5 months)

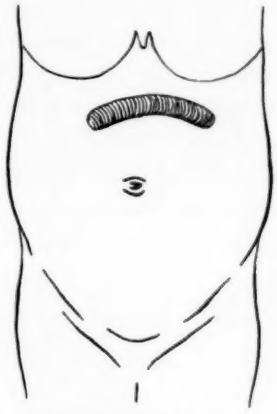

Fig. 5—Inv. Colic, 3 hours (♂ 9 months)

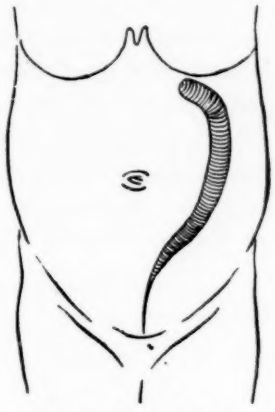

Fig. 6.—Inv. Colic, 2 hours (♂ 1 year)

in the transverse colon (Fig. 5). That the tumour is easily palpable in the rectum (Fig. 6) is natural and this was also the case of seven of my 16 patients with colic invagination. It is also true of the colic invagination tumours that their length bears no relation to the duration of the disease; the tumour in Fig. 4 for instance was due to an invagination which had lasted for 32 hours, while that in Fig. 6 had lasted only two hours.

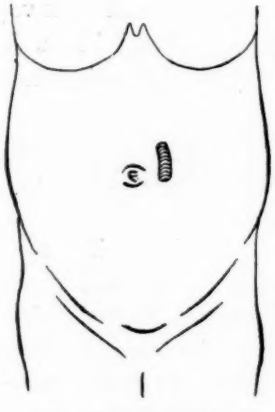

Fig. 7.—Inv. Iliac, 12 hours (♂ 1 year)

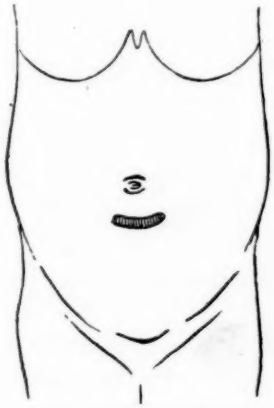

Fig. 8.—Inv. Iliac, 6 hours (♂ 6 months)

Iliac invaginations are always small, short, thin and very mobile tumours lying in the neighbourhood of the umbilicus (Figs. 7 and 8) and they can readily be moved forward under the skin and roundabout in the abdomen.

In over half of my *ileo-colic* invaginations I found a tumour of the size and in the situation shown in Fig. 9, thus one which is quite like that found in ileo-cœcal invaginations, but which is seldom as long as the latter. I have only one case in which the tumour was palpable in the rectum (Fig. 10);

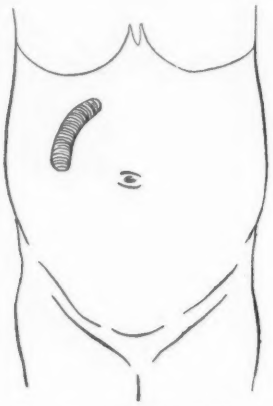

Fig. 9.—Inv. Ileo-colic, 9 hours (♂ 5 months)

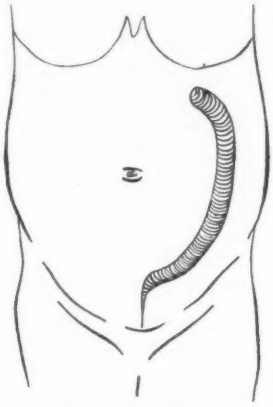

Fig. 10.—Inv. Ileo-colic, 12 hours (♀ 6 months)

this tumour was also only felt in the left side of the abdomen. I have only observed such a left-sided tumour in one other case of ileo-colic invagination, but the post-mortem examination showed that the cœcum was situated on the left side of the abdomen. Lastly, in three cases I found the tumour involving chiefly the transverse colon.

Diagnosis.

I have dealt fully with the four cardinal symptoms of these invaginations because it is of the greatest importance that they should be so impressed on the doctor's mind that he never overlooks an invagination or mistakes it for something else. When all the four symptoms are present no doubt ought to be possible; nor should there be doubt in a case where typical blood and slime are passed per anum in conjunction with an attack of colic and vomiting. The mistake that may sometimes be made is that the symptom-complex may be interpreted as the manifestation of follicular enteritis. In one of my patients the passage of blood was so great and such a dominating feature that the child was admitted by the doctor with the diagnosis: "*hæmorrhagia per anum, periculum in mora.*" On the other hand, it should be remembered that there are invaginations where typical blood and slime are not passed for 24 hours or more after the illness has begun, and lastly, as I mentioned above, there are invaginations where practically no bleeding occurs. That one must not allow oneself to be misled by the apparent well-being and calm appearance which the majority of children with intussusception display in the free intervals between the attacks of colic, cannot be too strongly emphasised.

Topical Diagnosis. When the diagnosis of invagination has been made the next question is whether one can decide from the clinical symptoms and physical signs what form of invagination one has to deal with. I am quite aware that such a topical diagnosis is difficult and needs some experience, but as it is of the greatest importance both for the prognosis of the disease and the treatment one ought always to try to get as near to it as possible. I will, therefore, briefly pass in review the factors which are most helpful to me in the differential diagnosis between the four chief forms.

In the *colic invagination,* the tumour usually lies in the left side of the abdomen, corresponding to the descending colon and has an almost vertical course; it can often be felt in the rectum. More rarely it is situated above the umbilicus, corresponding to the transverse colon. It is characteristic of all colic invaginations that they always cause hæmorrhage and that the passing of blood takes place immediately or, at all events, within six hours of the occurrence of the invagination.

Iliac invaginations are always small, short, thin and very mobile tumours. As a rule no blood is passed, but fever and malaise set in more quickly.

If these forms are therefore, as a rule, easy to diagnose, the difficulties are so much the greater when it comes to making a differential diagnosis between *ileo-cœcal* and *ileo-colic invaginations.* Definite conclusions can only rarely be drawn from the situation, shape and size of the tumour, as those found in these two forms are often quite identical. But I am of opinion that if a rounded or oblong swelling which is difficult to define, can be felt, deep down in the ileo-cœcal region one should always think of ileo-colic invagination. The so-called Dance's sign (an emptiness in the right iliac fossa which is said to be characteristic of ileo-cœcal invagination) has never been of help to me, but has, on the contrary, sometimes led me astray. The points which I make use of in the differential diagnosis, besides what was said above about the tumour itself, are: (1) in children under one year the ileo-cœcal is by far the commonest form, while the ileo-colic is more frequent in older children; (2) in the ileo-cœcal form bleeding usually occurs immediately or within 12 hours of the occurrence of the invagination, whereas in the ileo-colic form bleeding, as a rule takes place later, 12, 24, or 48 hours afterwards; (3) the ileo-colic form commonly causes more severe attacks of colic and more violent vomiting than the ileo-cœcal; and (4) in the ileo-colic form fever usually sets in more quickly and there is more malaise than in the ileo-cœcal variety.

With the aid of this information I believe that the correct differential diagnosis can often be made, but I will not disguise the fact that I have unfortunately sometimes failed.

Treatment.

I will now pass on to discuss the treatment. I will start by pointing out that the treatment of acute invagination of the intestine ought to be carried out only at a hospital.

When the practitioner has diagnosed intussusception, in fact, even if he only has a suspicion of it, he should immediately send the child to a hospital and not waste valuable time with narcotics and non-surgical attempts at reducing it at home. On this point I must very decidedly disagree with *Hirschsprung* and *Wichmann*, both of whom advocate the feasibility of treatment at home. Throughout Denmark admission to hospital is so easy and expeditious that there is no excuse for beginning to treat acute intestinal invagination in the patient's home.

But the question now is: What treatment shall the hospital doctor choose?

That reduction of the invagination by primary laparotomy is and must be the ideal treatment, all are agreed. But the fact is that this method of treatment in children in the first, and even in the second year of life, has been associated with a surprisingly high mortality almost everywhere throughout the world. No wonder, therefore, that attempts have been made to save a healthy child's life by non-surgical reduction of the invagination, and Hirschsprung, as is known, has gained imperishable credit for advocating the bloodless treatment. Encouraged by the results which I had the opportunity of seeing when I was Assistant Physician under Hirschsprung, I have naturally followed up this method, with what result will now be seen.

When the bloodless method of treatment is mentioned in the literature, water injections into the intestine are almost always spoken of (*Wassereinspritzungen*, irrigations, hydrostatic pressure, etc.), and there seems, therefore, to be a general impression that the bloodless reduction of an invagination is principally effected by injecting water into the intestine. Both Hirschsprung and Wichmann themselves are responsible for this view becoming so universal, for although they both employed and discussed the massage treatment, they conclude by laying the greatest stress on water injections.

That I, as a pupil of Hirschsprung, also at first attributed most importance to the action of water pressure goes without saying. But although this treatment led in many cases to the desired result I soon became aware that the method had its great drawbacks, and what specially worried me was that when water had been introduced into the intestine and the abdomen distended, the tumour could no longer be felt, and, moreover, it was naturally easily displaced by the water injection. One was thus prevented from following whether it became larger or smaller from the manipulations, and the massage was really applied haphazard. The method,

moreover, was inapplicable to small intestine invaginations, for water pressure treatment in these forms is ineffective. I, therefore, soon abandoned this procedure and placed more reliance on regular taxis.

The method I use is as follows. After the bladder and perhaps the stomach are emptied, the child is put deeply under an anæsthetic, for which purpose I always use chloroform, because I do not get the abdominal muscles so relaxed with ether narcosis as they necessarily have to be in order that regular taxis can be performed. When the child is unconscious I palpate the whole of the invagination swelling as accurately as possible and try to reduce it by going to work in the following manner.

If it is a *large intestine invagination*, an *ileo-cæcal* or a *colic* one, I first grasp the neck of the invagination with both hands and compress it for one or two minutes to diminish the œdema and blood extravasation. I then steady the neck with the left hand, take hold of the apex with the right hand and try to reduce the invagination by pulling the intussusception back through the intestine. Sometimes it can easily be reduced, at others it may be very difficult and needs considerable strength, but in no case do I persist in these taxis manipulations beyond 10 or, at most, 15 minutes.

If it is an *iliac invagination*, in which one cannot at first tell where the neck and head are, I grasp the two ends of the tumour and cautiously pull from each side alternatively, until I find that the invagination is reduced. In this form of invagination I never try taxis for more than five minutes. If by then the invagination has not shown the least sign of yielding there is a great probability that it is complicated by a polypus or a Meckel's diverticulum, and then only harm will be done by continuing the taxis.

After the taxis is finished, whether it is considered to have succeeded or not, I inject water into the intestine, using, as Hirschsprung does, an enema syringe and Oser's sound which are introduced as high up as possible. While an assistant compresses the nates around the sound, I pump in water with one hand and place the other one flat on the abdomen so as to judge the degree of distension. When this has become so great that water begins to ooze out of the anus at the side of the sound, I stop pumping and let the water run slowly out again.

Previously, I always gave two, three or four such water injections in succession; now I am usually satisfied with a single one or at most two, because as I have said, I place more reliance on dry taxis than on water pressure for reducing the invagination. But it is chiefly for other reasons that I always finish with a water injection. In the first place, one often obtains proof in this way that the invagination is reduced, namely, when on letting out the water fæcal particles come away with it towards the end. In the second place, by washing out with water, toxic substances which have accumulated above the site of the invagination are often got rid of, and thus the danger of intoxication is lessened. And lastly, by leaving some of the water behind in the intestine to be absorbed, the turgor of the tissues is increased and so the child's resistance is enhanced.

When the entire procedure (dry taxis and water injection) is finished, which usually takes 20 to 30 minutes, the child is put to bed with a binder round its abdomen; it is provided with hot bottles and, if necessary, receives camphor injections and subcutaneous injections of salt solution. Until the first motion is passed the child only receives boiled water to drink and in small quantities at a time. No medicine is given by the mouth and, in particular, I never give opium or purgatives.

Unlike Hirschsprung I never make more than one bloodless attempt at reducing the intussusception; if this fails I resort to laparotomy.

I will add that I have never seen rupture of the intestine occur as a result of this treatment. It is possible that in difficult cases of reduction where enormous force must often be used, rupture of the serous covering of the gut may take place, but it also happens now and again in operative reduction, and there are not many surgeons who attribute so much importance to these ruptures that they would lengthen the operation by suturing them. However this may be, I have, at any rate up to the present, never had a case of rupture of the intestine or peritonitis following bloodless taxis.

The bloodless treatment here described necessarily demands some practice, but it is perfectly straightforward to carry out and the majority of house physicians whom I have had in the course of years have rapidly acquired the technique and have performed many reductions of intussusceptions.

I now come to the question which is as important as it is difficult: Is the invagination reduced or not?

It is perfectly clear to me that we are here up against the " Achilles heel " of the bloodless treatment. This is the point which needs most experience and where a false conclusion is always fatal to the child's life.

When one has done taxis one will nearly always be able to feel a tumour of larger or smaller size at the place which corresponds with the neck of the invagination. To decide whether this swelling is the last unreduced part of the intussusceptum or merely the thickened wall of the intestine, needs a good deal of practice and experience. Particularly in the ileo-cœcal invagination, the cœcum, ileo-cœcal valve and mesenteric glands can be the seat of so much œdema and extravasation of blood after reduction of the invagination, that the whole region feels like a hard tumour the size of a walnut, which may well simulate the last remnant of the invagination. I admit that, especially in the early days, I frequently felt very much in doubt about the interpretation of such a tumour, but of late I think I can say that my judgment is usually right.

The criterion of whether the invagination is reduced or not, is, of course, whether the motions are passed. This is also the reason, as stated above, that I always give a water injection after taxis and make a careful inspection for particles of fæces in the water that comes away.

Altogether I have reduced 75 intussusceptions by bloodless taxis, and in these the times when the first motion was passed after reduction were as follows:—

TABLE V.

Immediately	after	taxis	...	33	cases.	16	hours	after	taxis	...	...	1 case.
1– 3 hours	,,	,,	...	12	,,	22	,,	,,	,,	...	...	2 cases.
4– 6 ,,	,,	,,	...	14	,,	30	,,	,,	,,	...	...	1 case.
7–12 ,,	,,	,,	...	11	,,	34	,,	,,	,,	...	...	1 ,,

As will be seen a motion was passed immediately in nearly half the cases, but often it was necessary to wait many hours. It is easy to understand that this period of waiting is often a very anxious and unpleasant one, but the trained observer will almost always be able to decide whether the invagination is reduced or not. The chief points to look for are whether the periodic attacks of colic return, whether the facial expression of the child again assumes the type which is characteristic of patients with intussusception and whether the passing of typical blood and slime per anum occurs afresh. But one must not be misled by the fact that very severe intoxication symptoms such as vomiting, high temperature, eclampsia, etc., can also occur after taxis has been performed, for this is not uncommon. Intoxication after a bloodless reduction of an invagination may even be so great that death ensues. Thus three died of the 75 children in whom I succeeded in performing a bloodless reduction. First, a girl of 7 months who had a colic invagination which had lasted for 29 hours, with a tumour whose size and position was about the same as that shown in Fig. 6. Reduction was simple, but she died 30 hours later with hyperpyrexia, and at the autopsy exhibited nothing beyond some ecchymoses in the sigmoid flexure, especially no invagination anywhere, no rupture of the intestine and no peritonitis. The second case was a girl 3 months old, with an ileo-cœcal invagination which had lasted nine hours (Fig. 2). In this patient also the invagination was easily reduced by the bloodless method, but she died three days later in a state of eclampsia. The third case was a boy, 5 months old, who had an invagination of nine hours' standing (Fig. 9). I thought I had to deal with an ileo-cœcal invagination and therefore performed bloodless taxis which succeeded, but he died after 24 hours with hyperpyrexia and eclampsia. No invagination, no rupture of the intestine and no sign of peritonitis were found at the autopsy, but it was seen that the invagination had not been an ileo-cœcal but an ileo-colic one, because the appendix and the mesentery were quite normal, and had, therefore, not been inside the invagination (preparation preserved). This last case is particularly interesting because it shows that it is really possible to reduce an ileo-colic invagination by the bloodless method. I shall not, however, allow this case to tempt me. Luck was here greater than intelligence, and I still firmly believe that if one has a suspicion that the invagination is an ileo-colic one, bloodless taxis must never be performed.

Results of Treatment.

In conclusion, I will give an account of the results of the treatment of my cases.

As mentioned in the beginning, I have had experience of a total of 115 cases; five of them, however, did not get any treatment because two were unrecognised and only discovered at the autopsy, and three were admitted moribund and died a few hours afterwards. I have, therefore, 110 treated cases.

Of these, 16 were *operated on primarily*, with the result that five were cured and 11 died. It goes without saying that this high mortality (68·8%) tells us nothing with respect to the prognosis of a primary operation, for it was only old and complicated cases that received surgical treatment primarily.

I have thus 94 *cases which were subjected to bloodless treatment.* Of these, 84 received *only* this kind of treatment, while ten had a subsequent laparotomy performed after taxis had failed. The results are:—

TABLE VI.

Taxis alone - - -	84—72 cured and 12 died	=	14·3 % mortality.
Taxis and Secondary Laparotomy -	10— 4 cured and 6 died	=	60·0 % mortality.
Total - - -	94—76 cured and 18 died	=	19·1 % mortality.

With regard to the secondary laparotomy, it has been asserted by many that this should always be done immediately and under the same narcosis as the taxis so as not to expose the child to repeated narcosis. It is possible that this view is correct in theory but it is impracticable, because it is often necessary to wait some hours before it can be decided whether taxis has been successful or not. Judging from my cases it does not appear that the prognosis of secondary laparotomy is worse when some time elapses between the taxis and the operation. Thus the four children who were cured by secondary laparotomy were operated on from 14 to 20 hours after taxis had failed, whereas in the six who died the operation took place only a few hours after.

Of my 84 non-surgically treated cases, 12 died, as stated. Of these, three children died from intoxication in spite of taxis being performed, while the remainder (nine cases) died without a secondary operation being undertaken, either because they were in such a bad condition that I dared not risk a laparotomy or because I erroneously believed that the invagination had been reduced.

The effect of the bloodless treatment in the different forms of invagination is seen in Table VII.

TABLE VII.

Of	19	Colic Invaginations	18	were cured	and	1 died	= 5·3 %	mortality.
,,	59	Ileo-Cœcal ,,	52	,,	,,	7 ,,	= 11·9 %	,,
,,	5	Iliac ,,	4	,,	,,	1 ,,	= 20·0 %	,,
,,	10	Ileo-Colic ,,	2	,,	,,	8 ,,	= 80·0 %	,,
,,	1	Mixed Form ,,	0	,,	,,	1 ,,	= (100·0 %)	,,

As will be seen from these records the bloodless treatment gives excellent results in the case of *large intestine invaginations*. I had altogether 78 large intestine invaginations and no less than 70 of these were cured, a death-rate of 10·25%, a mortality which is not only far smaller than that of the majority of surgical statistics, but can also compare with the very best results shown by primary laparotomy. In *Iliac invagination*, which always shows a serious prognosis, the bloodless method has also given very satisfactory results, for it was carried out with success in four out of five cases. Besides the rare mixed forms, the worst form is the *ileo colic invagination*, for I had ten cases, eight of which died, or a mortality of 80%. In all these cases I tried the bloodless treatment, because I wrongly supposed I was dealing with an ileo-cœcal invagination. One's efforts must, therefore, be directed towards perfecting the differential diagnosis between the ileo-colic and ileo-cœcal forms, a task which is by no means easy but which is of the greatest importance because, as I have mentioned above, the bloodless treatment must never be attempted in cases of ileo-colic invagination. That one must likewise never try this treatment if one has a suspicion that the case is a mixed form of invagination, goes without saying.

The forms of invagination in which it is permissible to try the bloodless treatment are therefore the *colic*, the *ileo-cœcal* and the *iliac*. But this must not be interpreted as meaning that the bloodless treatment should be tried always and in all cases in these three forms of invagination, for that must not be done. The child's age and the length of time the invagination has lasted must also be taken into account. A child over two years of age must, as a rule, never be treated by the bloodless method, but must immediately have laparotomy performed on it. With regard to the duration of the invagination, it depends on what form it is. Experience has gradually taught me to abide by the following rules.

In the colic form taxis may be tried provided that the invagination is not more than 36 hours old; in the ileo-cœcal form, when it is not more than 24 hours old; and in the iliac form when it is not more than 12 hours old.

On this point my cases show the following:—

TABLE VIII.

18	Colic Invaginations	under	36	hours	with 1 death.
52	Ileo-Cœcal ,,	,,	24	,,	,, 5 deaths.
4	Iliac ,,	,,	12	,,	,, 1 death.

These figures show a total of 74 cases of which only seven were fatal, that is to to say, *a mortality of* 9·5%.

These are the results of my 20 years' experience of the bloodless treatment of acute intestinal invaginations in infants. And if they are compared with the results of a primary operation I cannot but think that the bloodless treatment carried out in the right way and in accordance with the proper indications also has its legitimate sphere of usefulness.

EFFECTS OF SCARLET FEVER ON RHEUMATIC SUBJECTS.

BY

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In the practice of a large fever hospital one is constantly meeting cases of scarlet fever with a history of previous rheumatism. In this paper an attempt is made to give a brief account of all cases of scarlet fever with cardiac complications, occurring in this hospital over a period of one year.

In all, 47 cases showing cardiac symptoms have been considered, and of these, seven had a definite history of rheumatism.

During the period observed, the percentage of scarlet fever cases which developed cardiac symptoms was 0·55%, while in every case in which there was a previous history of rheumatism there was definite cardiac affection. Indeed, judging from the experience of many hundreds of cases of scarlet fever extending over a period of nearly three years, it can be stated that almost without exception an attack of scarlet fever in a rheumatic subject is followed by a reappearance of some of the symptoms associated with rheumatic infection.

The seven cases with a previous history of rheumatism will be taken first.

Case 1. B. H. Female. Aged 10. Admitted 6.2.25. Had been an in-patient of the Bristol General Hospital two years previously suffering from wasting and chorea. The attack of scarlet fever was mild but quite typical. On admission temperature was normal, pulse 100. There was a faint blowing systolic murmur in the aortic area, which was invariable throughout her stay in hospital. On the 32nd day of disease however there was a slight rise of temperature and the patient developed an irregular pulse and a blowing systolic murmur in the mitral area. There was no arthritis during the illness. The mitral systolic bruit had greatly diminished and the cardiac rhythm was normal when the patient was discharged 14 days later at the parents' request.

Case 2. C. W. Female. Aged 14. Admitted 22.5.25. This child had been admitted to the Bristol General Hospital suffering from chorea and while there had developed a rash. This was a moderate case of scarlet fever. On admission temperature was normal, pulse 76. The cardiac sounds were normal and the point of maximum cardiac impulse was in the nipple line between the fifth and sixth ribs. Fifteen days later temperature rose to 101·2°, pulse 104. The cardiac rhythm was irregular, maximum cardiac impulse half an inch outside nipple line, with a loud conducted apical systolic bruit. Six weeks later when the patient was discharged, the maximum cardiac impulse was in the nipple line, pulse 72 regular, and the apical systolic bruit was still well marked.

Case 3. Female. Aged 17. Admitted 28.10.25 with mild scarlet fever. Had rheumatism twice previously. There was an occasional cardiac irregularity on admission, temperature 100°, pulse 104. Fifteen days later the patient developed a faint apical systolic bruit. There was no accompanying rise of temperature. In ten days the bruit had completely disappeared.

Case 4. A. W. Male. Aged 9. Admitted 4.1.26 with scarlet fever of moderate severity. History of several attacks of chorea previously. The heart showed a diffuse heaving impulse, with the point of maximum cardiac impulse in nipple line. Soft blowing apical systolic bruit conducted towards axilla. The temperature remained normal after the first day and the cardiac signs diminished but did not disappear, pulse about 92 throughout. Twenty-six days after admission temperature rose suddenly to 102°, pulse 144, and the cardiac bruit became much louder and harsher. This was accompanied by a sore throat and the presence of a septic spot on the left tonsil. Six days later the patient was discharged at the request of the parents and against advice. The patient died seven days from discharge.

Case 5. L. W. Female. Aged 25. Admitted 16.2.26, with a moderate attack of scarlet fever. Rheumatic fever three years previously. On admission temperature was normal, pulse 80. There was a blowing diastolic murmur heard best along the left sternal border. No irregularity of rhythm. First sound fair. Twenty days after admission the temperature which had hitherto been normal commenced to vary between 97 and 99·5°, pulse 100. A faint apical systolic bruit in addition to the diastolic bruit was heard. These sounds still remained when the patient was discharged three weeks later.

Case 6. L. C. Female. Aged 48. Admitted 2.3.26 with a moderate attack of scarlet fever. Had rheumatic fever 20 years before, and had no cardiac symptoms since. On admission temperature 102°, pulse 124 (irregular). Short presystolic murmur and poor first sound. Joint pains. For 14 days there was marked irregularity of rhythm and a few creps at both bases. Seven days after admission a systolic murmur appeared. A diastolic murmur was heard a week later along the left sternal margin. At the time of discharge the general condition was good but the cardiac bruits, although fainter, still persisted. There was also less irregularity.

Case 7. E. B. Female. Aged 34. Admitted 5.3.26, fourth day of a very mild attack of scarlet fever. Rheumatic fever 18 years before. Several attacks since. Temperature normal on admission, pulse 84. Heart—heaving diffuse impulse, point of maximum impulse fifth space in nipple line. Marked presystolic murmur. Weak second sound. There was no rise of temperature during period in hospital and the cardiac murmur was slightly less marked on discharge. Pulse 88.

Of the 40 cases of scarlet fever with no previous history of rheumatism which developed cardiac symptoms, 12 still had symptoms on discharge. In the remainder the symptoms entirely cleared up. In quite a fair proportion of cases, therefore, scarlet fever, like rheumatism, leaves a lasting impression upon the heart. It has not been possible to ascertain whether the symptoms have disappeared after discharge. In six cases there were abnormal cardiac sounds on admission (*i.e.*, in the early stages of scarlet fever) and it is quite possible that some of these cases had a previous rheumatic history which was not obtained or obtainable from the relatives. Seven of the 40 cases had definite arthritis. Twelve had chronically enlarged tonsils.

In all those cases with no previous rheumatic history the symptoms were much less severe (cardiac bruit, increase of cardiac dulness, rate of respiration, etc.).

It would appear, therefore, that the almost invariable result of scarlet fever upon a heart already damaged by rheumatism is a rekindling of the old trouble which in some cases had been quiescent for a considerable period (in Case 6, for 20 years). Further, a mild or moderate attack of scarlet fever is quite capable of bringing this about.

In view of the more than probable common streptococcal origin of the two diseases, the equally probable common port of entry of infection, the striking similarity of many of the symptoms, and their response to like treatment, it is thought that this short account of a small number of cases combining these two diseases may be of interest.

My grateful thanks are due to Dr. B. A. Peters, Senior Resident Medical Officer, Ham Green Hospital, Bristol, for permission to use the hospital records.

SOME EXPERIMENTS WITH HÆMOLYTIC STREPTOCOCCUS TOXIN OF VARYING ORIGIN IN CONNECTION WITH THE "DICK" TEST FOR SCARLET FEVER.

BY

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In view of the somewhat varying estimates which have been attached to the value of the readings obtained, up to date, by means of the " Dick " test on children, the following controlled series carried out mostly at the Children's Hospital in Paris, and in the case of Series III at the West London Hospital, may be of interest.

When Drs. G. F. and Gladys Dick announced, in 1923, that in their opinion the short-chained hæmolytic streptococcus which, on many previous occasions, different observers had obtained from the throats of scarlatinal cases was in fact the causal agent of the disease, they apparently confirmed the findings of Klein, Tunnicliff, Mervyn, Gordon and others. Since, however, it would seem probable that several strains of this microörganism, differing in virulence, have been isolated, it would appear desirable when employing various samples of scarlet fever toxin for test and diagnostic purposes, to know something of their antecedents if we are to correlate the clinical results obtained by their use.

The Dicks' streptococcus exhibits no distinguishing characteristics by which it may be recognised with certainty in the test tube or under the microscope, their original test consisting in injecting small quantities of the toxin of the suspected organism mixed with antitoxic serum; and of the toxin alone, into susceptible individuals. Apart from this test the organism was described as being an hæmolytic streptococcus of which the colonies measured about 2 mm. in diameter, with an hæmolysed area of about 4 mm. It produced acid with dextrose, maltose, glucose, lactose and milk, and varied with mannite; it had no action on inulin[1].

Their toxin was prepared by passing the liquid medium, after four days, through a filter paper until clear, then through Berkefeld filters. The toxins used by the present writer were prepared by Dr. Gory at the Pasteur Institute, in similar fashion, and standardised; Cultures I and II being isolated from the tonsils of children with typical scarlet fever, before the fifth day of illness. Both these cultures presented similar characteristics.

Culture III was received from Dr. Anna Williams of the Public Health Department of New York, and appeared to have been isolated for some time, since it presented certain degenerative characteristics.

Culture IV (Dochez) was kindly supplied by Dr. O'Brien, from the Wellcome Physiological Laboratory, and had been carefully compared with a standard toxin.

The following "pedigree" will serve to distinguish them:—

TOXIN I.—(a) (No. Rl5 Inst. Pasteur) from culture grown on Martin's broth for 3 days.
(b) „ „ „ „ „ „ 6 days.

TOXIN II.—(a) No. Sl5 Inst. Pasteur) from culture grown on blood broth for 7 days.
(b) „ „ „ from culture grown on Martin's broth for 7 days.

TOXIN III.—(a) (Williams) from culture grown on blood broth for 3 days.
(b) „ „ „ „ „ „ „ 6 „

TOXIN IV.—(R.A.O'B.) made according to method described by Dr. Okell and colleagues.

CULTURAL CHARACTERISTICS.

Cultures I. and II. and III.—In ordinary bouillon these cultures gave an abundant growth. The medium was clear with, later, finely granular masses. On gelatine slopes, small slightly translucent gray colonies were seen, with fairly regular contours, which were in parts finely dentate. On ascitic fluid medium and blood gelatine plates the colonies were typical, and gave, in 24 hours, an obvious zone of hæmolysis which was sharply defined for 2-3mm. Cultures I. and II. curdled milk in less than 24 hours, the clot being fissured from second day, and the fluid clear. In the case of III., clot only appearing after heating to 100°C. for three minutes.

Gelatine at varying pH incubated at 22°C., was liquefied by I. after 24 hours at pH 7·4, 6·5, and 6·0. II. was not tried, and III. failed to liquefy it.

All these cultures were without effect on Inulin.

Culture IV.—This culture was produced from an hæmolytic streptococcus of strain "Dochez." It gave acid with milk, and was without action on Inulin and Dulcite.

ACTION ON SUGARS.

Culture	I.	II.	III.	IV.
Glucose ...	+	+	+	+
Maltose ...	+	+	+	+
Lævulose ...	+	+	+	
Lactose ...	+	+	+	+
Saccharose ...	+	+	+	+
Mannite ...	0	0	0	+
Dextrin ...	0	0	0	+
Xylose ...	0	0	0	
Salicin ...				+

The hæmolytic action of the filtered toxin was tested with a 24-hour culture; Culture I. yielding a fluid producing hæmolysis more rapidly, and in higher dilutions, than the other cultures.

METHOD EMPLOYED.

As will be seen by reference to the Tables below, each toxin was injected in varying dilutions, the dose, unless otherwise stated, being 0·2 cc.

A control consisting of the same dose of one of the toxins which had been heated for one hour at 100° C. in a water-bath was used in every case. The same group of children in a general ward of the Hospital (Enfants Malades) in Paris, was used; in each case the von Pirquet reaction was negative.

In the English series (III) the toxin supplied by Dr. O'Brien was used at the same time as the French Toxin II (a) and (b) and under the same conditions.

All results were read 24 hours after injection, and the following symbols only are used. Positive (+)=red area 1-2 cms. in diameter. Slight positive (±)=distinct red colour up to 1 cm. in diameter. Pseudo and combined reactions are, for convenience, recorded as positive or negative. There were no strongly positive reactions (over 2 cms.).

SERIES I.

		I. (a)	I. (b)	II. (a)	II. (b)	III. (a)	III. (b)
1	a	±	N	+	+	+	N
	b	+	N	+	N	+	N
2	a	N	N	N	N	N	N
	b	N	N	N	N	N	N
3	a	N	N	N	N	N	N
	b	N	N	N	N	N	N
4	a	N	N	N	N	N	N
	b	N	+	+	+	+	N
5	a	N	N	N	N	N	N
	b	N	N	N	N	N	N
6	a	+	±	N	N	N	N
	b	+	N	N	N	±	N
7	a	+	±	+	N	N	N
	b	N	N	±	N	N	N
8	a	N	N	N	N	N	N
	b	N	N	N	N	N	N
9	a	+	+	+	+	+	+
	b	+	+	+	+	+	+
10	a	N	N	N	N	N	N
	b	N	N	N	N	N	N

(a) = 1 : 1,000. (b) = 1 : 5,000.

It will be noticed that the results with the six toxins used in this series are by no means in accord with each other. The chief point of interest would appear to be the varying results recorded in the case of different dilutions of the same toxin in these children, the positive not invariably being registered by the toxin in the lower dilution.

Toxin II from the culture grown in Martin's (peptone) broth gave less positive results than that grown in blood broth; while in the case of Toxins I and III, it appears to be the younger culture (three days' growth) whose toxin proved the more active.

Toxin No. II (a) was next injected in two weak dilutions, with a control, into a series of infants ranging in age from 21 days to 11 months; the dose in this case being 0·1 cc.

SERIES II.

No.	Age: Months	1 : 100	1 : 500
1	8	N	N
2	9½	+	+
3	3½	N	N
4	7½	N	±
5	10½	+	±
6	2½	N	? N
7	8	+	±
9	21 days	N	N
10	8	N	N
11	6	N	N
12	4½	N	+
13	6½	N	N
14	11	±	±
15	4½	N	N

According to most authorities, infants below the age of 5 and 6 months retain a transmitted placental immunity. In No. 12 of this series it will be observed, however, that a positive result was obtained at the age of 4½ months. The parents were, unfortunately, unavailable for testing purposes. Again it is seen not to be the stronger toxin which invariably recorded the positive reaction in a doubtful case at this age.

In Series III which was undertaken by kind permission of Dr. Arthur Saunders, toxin supplied by Dr. O'Brien (IV) was employed in conjunction with the French toxin, No. II (a) with the following results:—

SERIES III.

	IV. 1 : 5,000	IV. 1 : 1,000	II. (a) 1 : 5,000	1 : 1,000
1	±	±	±	+
2	N	N	N	N
3	±	N	N	N
4	+	+	+	+
5	N	N	N	N
6	N	N	N	N
7	N	N	N	N
8	+	+	+	+
9	N	N	N	N
10	+	+	+	+

Here it will be seen that in Case 1, whilst the lower dilution of the French toxin gave a definite +, the other three yielded ± results. In Case 3 the reactions are in the reverse direction.

The high percentage of negative reactions observed in these series is due to the fact that some of the children tested had doubtless suffered with scarlet fever. This was, however, ignored since positive results were not the object of testing—the comparison of results being the primary object of the series.

CONCLUSIONS.

It was found in the course of the small series of trials of the "Dick" test with toxins of various origins and strengths, that anomalous results were in some cases recorded. These results did not appear to be accounted for by lack of standardisation of the toxins, so much as by lack of standardisation of the strain of the original streptococci employed, and the methods and time employed in culturing them. Brown[2] states in a recent paper that he found that the use of different dilutions of toxin may show divergent results. He found, however, that the positive result would always be given by the stronger toxin, a finding which was not entirely borne out in the present series. Experimental error must, of course, be allowed for, and also variations of the personal equation as regards interpretation of results. Possible error in this direction Park estimated at about 2%.

It is of interest to note that a positive Dick reaction was found in a child of 4½ months of age; this, however, has previously been recorded; amongst others, by Rosen and Korobincina of Moscow[3].

If the foregoing results be accepted, it would accordingly seem desirable to arrange for (a) an internationally standardised strain of scarlet fever streptococcus to be procurable for purposes of obtaining "Dick test" toxin; (b) a standard method of culture of the organism (*i.e.*, time, medium, etc.); and (c) a standard method of preparation of the toxin, if experimental results from different sources are to be correlated accurately.

I must, in conclusion, thank Professor P. Nobécourt and Dr. Max Lévy for giving me all facilities in France, and Dr. Arthur Saunders for permission to publish Series III.

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THE CREATININE COEFFICIENT IN THE INFANT.

BY

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The urinary excretion of creatinine in the adult both in health and disease has been extensively studied. In infants, however, data concerning the urinary output of this important endogenous catabolite are still incomplete. Investigations on this line therefore are called for, since they might prove of value for a better understanding of both the physiology and the pathology of the infant.

Until Folin developed his method for quantitative determination of creatinine there was much difference of opinion whether creatinine did exist in the urine of the infant or not. In 1905, however, von Hoogenhuyze and Vorploegh[1] were able to show that creatinine was constantly present. In a few infants they made quantitative estimations and found the values to vary between 0·41 and 1·7 mg. per 10 c.cs. of urine, the lower figure being in a weak artificially-fed baby. Lesné and Binet[2], on the basis of a study of 13 cases, state that the total creatinine output in infancy increases with age, varying between 1·4 and 19·0 mg. per kg. of body-weight in 24 hours. Their results are expressed as per volume of urine and are rather inconstant. In a recent publication[3], studying the day and night creatinine excretion, I have shown that in infants the creatinine output is quite independent of the volume of urine voided and consequently the above results cannot be accepted as a basis for any quantitative estimations.

Funaro[4], in a study of a few subjects, finds that the urinary creatinine in infants varies between 4·6 and 10·8 mg. per kg. of body-weight in 24 hours. He does not think however that excretion is affected by the nutritional condition of the infant. Amberg and Morrill[5], in a study based on 24-hourly urine collections, find in five new-born infants that the creatinine output ranges between 6·71 and 9·94 mg. per kg. of body-weight in 24 hours. Utheim[6] in 1921 studied 19 infants, two of whom were normal, the others suffering from various morbid conditions and most of them athreptic. Her figures for creatinine output expressed in terms of body-weight show wide variations and are somewhat lower for underweight infants. However, the two normal infants she observed yielded 9·1 and 10·5 mg. of creatinine per kg. of body-weight in 24 hours.

In a previous paper[7], and concurrently with the question of uric acid excretion in the infant, I have dealt with the rate at which creatinine is eliminated in the urine. The cases studied comprised both normal and undernourished infants. It was found that in both groups, *i.e.*, the normal and underweight infants, the creatinine elimination showed itself to be closely related to the body-weight and independent of the age, except in so far as weight and age are connected. When expressed in terms of body-weight the creatinine output ranged between 10·2 and 15·9 mg. per kg. in 24 hours. Although the values obtained did not show a very wide variation it was observed nevertheless that the higher values were generally found in the infants in a poor nutritional condition.

It will be seen from the above review of the previous work that the data concerning this subject are scanty and that there prevails considerable difference of opinion and findings. It was on this account that the present work was undertaken in an effort to estimate more accurately the relationship of the creatinine output to the weight of the infant and to evaluate, if possible, the creatinine coefficient as defined by Schaffer as a measure of the state of muscular development.

The cases reported in the present study were selected from the wards of the Royal Hospital for Sick Children, Glasgow. The infants were in varying state of nutrition, but none of them showed evidence of any acute gastro-intestinal disturbance or of the so-called specific diseases (syphilis or tuberculosis) or of fever[8]. To secure similarity of conditions the infants selected were all in the first year of life, so that there was agreement in diet, habits and physiology in general. Their nutritional condition is expressed in percentages of expected weight (normal weight for age) using Holt's[9] figures of weight for age. All the subjects had the usual and similar nursing care and in nearly all instances the diet was whole cow's milk, which is the standard feeding of the clinic; in a few cases milk modifications were employed. The caloric intake was regulated according to individual requirements and the feeding was unchanged for several days before and during the experiments. The infants were weighed before and after the period of study and the weights recorded are an average of these two estimations. For urine collections Findlay's method[10] was used. Urine samples were collected for two 24-hourly periods in order to serve as a check for quantitative collections and also to lessen the possible error due to any differences in the amounts of urine evacuated from the bladder and actually excreted by the kidneys. This made possible the exclusion of cases of inaccurate collections. Urine was preserved on ice and by adding toluol. Creatinine estimations were done on the day following collections, using Folin's[11] colorimetric method. The details of the findings are shown in the following table:—

TABLE I.

All urinary specimens were collected for two consecutive 24-hour periods.

Case:	Age (weeks)	Body-weight	% of expected weight	Urine c.cs. in 24 hours	Creatinine in Mgs.			Case:	Age (weeks)	Body-weight	% of expected weight	Urine c.cs. in 24 hours	Creatinine in Mgs.		
					Total in 24 hours	Per kg of body-weight	Coefficient						Total in 24 hours	Per kg of body-weight	Coefficient
1	32	8·75	110	472 414	80·4 82·8	9·2 9·4	3·5	15	48	6·90	72	794 723	83·6 80·6	12·1 11·7	4·5
2	16	5·80	93	235 305	72·0 67·8	12·5 11·6	4·6	16	33	5·90	72	498 645	71·3 73·5	12·1 12·4	4·7
3	27	6·92	91	572 385	76·5 81·1	11·0 11·7	4·2	17	9	3·40	70	306 357	46·4 46·2	13·7 13·6	5·2
4	22	6·37	90	990 1116	67·3 72·8	10·5 11·4	4·1	18	12	3·90	68	420 455	45·9 49·2	11·8 12·6	4·6
5	52	8·62	89	630 703	108·3 110·6	12·5 12·9	4·8	19	49	6·40	67	124 172	77·4 75·5	12·1 11·8	4·5
6	35	7·05	84	690 738	90·4 96·4	12·7 13·7	5·0	20	21	4·54	66	232 202	48·5 48·4	10·7 10·7	4·1
7	34	6·85	83	559 512	72·7 74·1	10·6 10·8	4·1	21	20	4·15	61	380 423	52·7 56·1	13·0 13·5	5·1
8	25	6·01	82	540 586	67·1 70·2	11·1 11·6	4·3	22	20	4·03	59	245 384	49·9 53·7	12·4 13·4	4·9
9	6	3·50	81	351 322	38·5 36·1	11·0 10·3	4·1	23	49	5·50	57	330 555	72·6 68·7	13·2 12·5	4·9
10	37	6·90	80	897 785	89·6 92·4	13·0 13·4	5·0	24	13	3·40	55	291 268	33·6 35·7	10·1 10·6	3·9
11	33	6·35	79	523 552	96·0 91·3	15·1 14·4	5·6	25	11	2·78	51	332 268	36·8 39·8	13·2 14·3	5·2
12	8	3·52	77	490 380	44·3 46·1	12·3 13·1	4·8	26	14	3·03	50	152 204	42·6 39·1	14·0 12·9	5·1
13	6	3·25	75	327 351	38·3 42·5	11·8 13·0	4·7	27	21	3·40	49	244 267	41·6 39·3	12·2 11·6	4·5
14	48	7·10	74	655 642	99·6 96·9	14·0 13·6	5·2	28	18	2·50	38	105 196	28·6 30·0	11·4 12·0	4·5

All the subjects of these investigations were fed on cow's milk, *i.e.*, a diet practically creatinine-free, consequently we are dealing with creatinine of endogenous origin. Again, they form a group which is homogeneous as regards feeding, habits, routine life and physiology in general, but whose main differences are those of age and nutritional state. This condition obviously directs our investigation to the finding out whether, and if so to what extent these two differentiating factors, age and nutritional condition as expressed in terms of body-weight, are related to creatinine output.

Infancy is the period of life in which age plays the most important rôle. There is no age during which not only morphological and anatomical but physiological changes occur with such rapidity as during infancy and early childhood. The infants studied ranging in age from 6 to 52 weeks thus provide a group in which these changes are most marked.

A review of the values as shown in the Table No. I. for total 24-hourly creatinine output as compared with age will show that age *per se* is not the determining factor. Variations are observed in the total creatinine elimination, but they would seem to be due to some factor other than age. For example, Cases 2, 7 and 19 are respectively 16, 34 and 49 weeks old, yet the total daily creatinine output on two successive days is found to be respectively, 72·0 and 67·8 mg.; 72·7 and 74·1 mg.; and 77·4 and 75·5 mg. That infants of such varying age should excrete amounts of creatinine which are approximately so equal is one of the most striking features of all our work on this question.

Having thus ruled out any connection between the age of the infant and the creatinine elimination there remains for consideration the question of body-weight. But before proceeding to the analysis of the results from this point of view it seems useful to review the literature concerning the origin and significance of the urinary creatinine and to state the prevailing opinions.

Folin[12] first established the fact that the rate of creatinine excretion is an index of the level of endogenous nitrogen metabolism. This conception is generally accepted although some authors still believe that a small portion may be converted into urea[13]. Schaffer[14], on a basis of extensive studies, finds that the creatinine output is directly proportionate to the muscular development and the power of an individual. He advances the opinion that creatinine is derived by some special process of catabolism taking place largely, if not entirely, within the muscle. This view finds confirmation in further studies of Folin and his co-worker, Denis[15]. Benedict and Mayers[16], on the other hand, while observing the creatinine excretion to be related to the body-weight, find no constant ratio between the creatinine output and the muscular development of the subject. It is to be noted that all these studies were done in the adult.

A survey of the cases included in the present study as shown in Table No. I. gives ample evidence that there is a close relationship between the body-weight of the infant and the daily creatinine output. The values obtained in practically all the cases of the group vary within very narrow limits—10·1 and 13·7 mg., though 9·2 and 15·1 mg. are the extremes. It is of interest to note that the lowest value was obtained in the case of an overweight infant, which observation is in accord with Folin's statement that fat persons yield less creatinine per unit of body-weight than do lean persons.

According to Cathcart[17] a normal adult yields as much as 30 to 40 mg. of creatinine per kg. of body-weight in 24 hours. Infants thus show a marked difference as it is seen that their excretion amounts to decidedly less than half (10-13 mg.) of that amount. How can this apparent difference in creatinine metabolism be explained? Sufficient evidence has been accumulated to show that creatinine is produced entirely within the muscle and in this connection it is important to bear in mind that the proportions of the various body-tissues are different in the infant and in the adult. While the infant's body is relatively rich in water and fat and poor in muscle, the proportion of muscle in the adult is high. It is computed that muscle forms 47 per cent. of the body-weight of the adult but only 23 per cent. of that of the infant. Thus weight for weight the infant has just one half of the creatinine yielding tissue (muscle) possessed by the adult. Schaffer, assuming that urinary creatinine is formed wholly in the muscle and that the muscular tissue constitutes about half of the body-weight in the adult, estimates that on the average 50 mg. of creatinine are formed by one kilogram of muscle per day. Applying this computation of Schaffer, which is based on lower values for creatinine output than these given by Cathcart, to two cases of our series, one of them 93 per cent. and the other 38 per cent. of expected weight, and thus representing the two extremes in nutritional state, the theoretical creatinine output as compared with the observed output is as shown in the following table :—

Case	Body-weight	Percentage of expected weight	Amount of Muscle = 23 % of body-weight	Creatinine output in 24 hours	
				Observed average of two days	Theoretical = 50 mg. per kilo of muscle
2	5·80	93	1,334 grms.	69·9	66·7
28	2·50	38	575 grms.	29·3	28·75

This striking agreement between the actual and the theoretical findings surely points clearly to the fact that in wasting in infancy the loss of muscle is in direct proportion to that of the other tissues, and thus opposed to the conclusions drawn from the study of basal metabolism. This hypothesis

is further substantiated by a prolonged study of a recovering underweight infant:—

A.L. Male. Aged 10 weeks. Admitted June 26, 1926. Weight on admission 2·70 kg. The history was the usual one of a non-thriving infant. Healthy at birth, weighing 3·40 kg.; never breast-fed; vomiting often expulsive in character since first week of life, latterly diarrhœa. On admission, stools normal, but vomiting severe.

The clinical findings were negative, except that the case was that of a small wasted infant, and the diagnosis was improper and irregular feeding. In the first 24 hours peptonised milk was given, then whole cow's milk which was continued during the whole period of study. Vomiting stopped within two days and the infant rapidly improved and increased steadily in weight. Creatinine estimations were done weekly.

The full data are seen in the accompanying table:—

TABLE II.

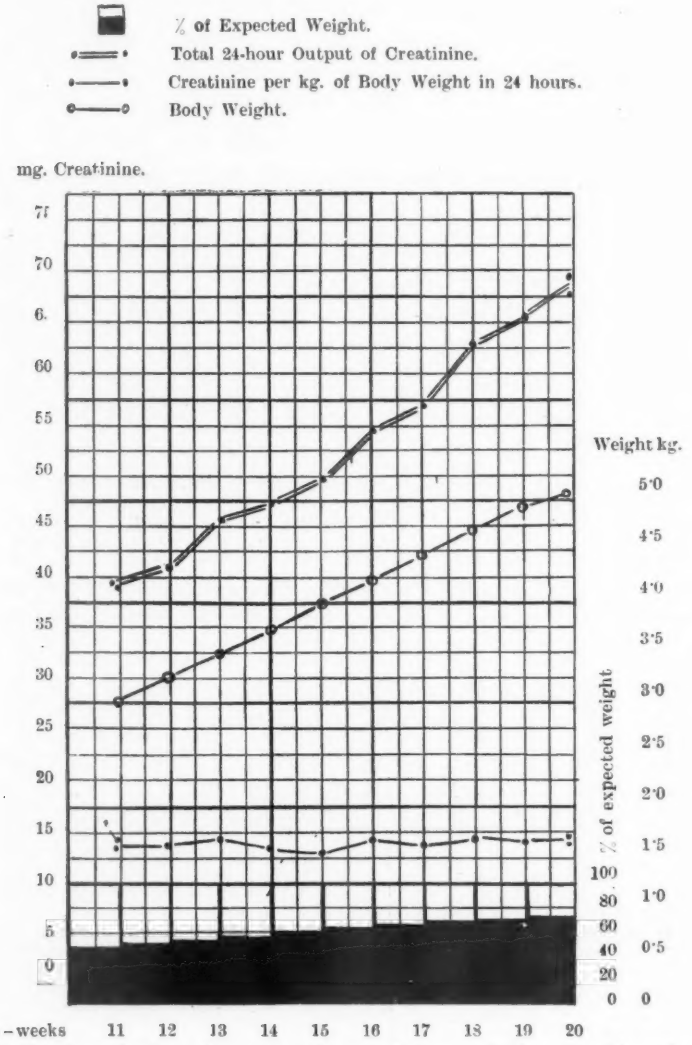
On the first and last occasions for purposes of control urine was collected for two successive 24-hour periods.

Age (weeks)	Feeding—whole cow's milk—calories	Body-weight kg.	% of expected weight	Urinary output c.cs.	Creatinine	
					Total in 24 hours	Per kg. of body-weight
11	192	2·78	50	332	38·8	13·9
—	456			268	39·8	14·3
12	456	3·00	53	381	41·3	13·7
13	456	3·23	56	377	45·6	14·1
14	504	3·52	58	460	46·9	13·3
15	504	3·74	60	409	49·2	13·1
16	504	3·90	62	357	54·7	14·0
17	558	4·19	65	492	57·1	13·6
18	558	4·45	68	503	63·3	14·2
19	558	4·70	70	430	66·2	14·1
20	558	4·80	71	230	69·0	14·4
				184	67·1	14·0

The striking feature of the results obtained in the case is that parallel with the remarkable gain in weight there is a rise of total 24-hourly creatinine output and that quite irrespective of the volume of urine voided. Also, even if the age factor had not been ruled out as a factor determining the daily creatinine output, the short period of time within which parallel changes in body-weight and creatinine output occurred is impressive, although characteristic of the age of infancy. The constant ratio between

the body-weight and the rate of creatinine elimination shown by the subject is to our mind strong confirmation of our view of the question. The chart given below shows the facts graphically.

CHART I.—BABY A.L.



Much study has been given to the problem of the wasting infant and the question has often been raised of the relative parts that the disappearance of the different tissues play in the loss of body-weight. Presumably, and especially in the condition of acute dehydration, there is first of all a relatively greater loss of water; adipose tissue is probably the next affected. Fleming[18] in his study of basal metabolism in the athreptic infant advances the opinion that in the first or slighter degrees of wasting, in fact till the infant has lost 35% of his weight, the reduction of body-weight occurs at the expense of metabolically inactive tissue—water and fat—and that it

is only when the fall in weight increases beyond this level that active metabolic tissue or muscle is lost. It would seem to us that in the present study there is a good opportunity of testing this hypothesis if one assumes that urinary creatinine is a measure of the amount of muscular tissue.

It will be seen from the table that the nutritional state of the infants studied has been indicated by percentages of expected weight. It will also be observed, as already stated, that the figures for creatinine output per kilogram of body-weight in 24 hours remain practically constant in all the infants in the group, except that perhaps in the series of cases, which are between 60% and 80% of expected weight, the variations are somewhat greater. On the basis of these results we feel justified in concluding that at any stage of wasting in an infant the reduction of muscle tissue as indicated by creatinine output is apparently parallel with the loss of total body-weight. In moderate degrees, however, there may be relatively a slightly greater loss of " dead " tissue, as is evidenced by the greater varying values obtained for creatinine excretion in these cases. It is, of course, just in these degrees of nutrition that there may be a greater variation in the relative amounts of water and fat, which would explain the wider variations in the figures obtained.

Arguing from the premise that there is a close relationship between the muscular development of an individual and the amount of creatinine excreted Schaffer[19] established his " Creatinine Coefficient," which represents the number of milligrams of creatinine nitrogen eliminated per kilogram of body-weight in 24 hours. This coefficient is considered to be the index of muscular development and power of a subject, and is estimated (Schaffer) to vary for an adult man between 8 and 11. Tracy and Clark[20] in agreement with this conception find this coefficient in adult women to be lower, on an average 5·8. We have computed in our cases that the coefficient in infancy ranges between 3·5 and 5·6, the lower value being obtained for an overweight infant. The average creatinine coefficient in the infant is found to be 4·6, *i.e.*, half of that in the adult, but as we have already remarked that relatively the muscular tissue in the infant is also only one-half of that of the adult, the low ratio in the infant is easily understood.

Résumé.

The rate of creatinine excretion in 28 male infants between the ages of 6 and 52 weeks and in varying nutritional condition ranging in percentage of expected weight between 38 and 110 was studied. The main findings were as follows:—

1. The daily creatinine elimination being constant is entirely independent of the age of infant.

2. The daily creatinine output in all the infants is found to be closely related to the body-weight and practically independent of the nutritional condition.

3. Using the evidence regarding the origin and significance of the urinary creatinine it was found that in wasting the reduction of active (muscular) tissue is parallel with the degree of wasting or total loss of body-weight.

4. A case of an undernourished infant studied for a longer period of time beginning with a nutritional state of 50% of expected weight until the infant through a remarkable and rapid improvement reached 71% of expected weight gives full confirmation to the above expressed statement.

5. The creatinine coefficient as an index of muscular development of the infant was determined and was found to be on an average 4·6, as compared with that in adult (male :—8-11, and female :—5·8) thus indicating the relatively poor development of the muscular system in infancy.

I wish to acknowledge my indebtedness to Professor Leonard Findlay for his kind help and invaluable criticisms.

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EFFECT OF ENCEPHALITIS LETHARGICA ON THE INTELLIGENCE OF CHILDREN.

BY

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I.—Introduction.

Disturbances of mentality are probably the commonest and most striking of the after-effects of encephalitis lethargica. Duncan[8] found mental sequelæ in 72% of his patients, Riddoch[6] in 70%, and Abrahamson[20] in 50%. They vary enormously in form and intensity: depression, melancholia, apathy, mania, pathological optimism, mental deficiency, loss of memory, inability to concentrate, change of disposition (which is always for the worse), irritability, bad temper, destructiveness, cruelty, and moral perversity (which usually takes the form of stealing, lying, or swearing) are among the most frequently occurring[6] [8] [12] [20]. The severity of the disturbance varies from slight loss of emotional control or slowness of mental response to acute dementia or idiocy[6]. It appears to be higher among children than among adults. Duncan[8] found that the percentage of his cases with mental sequelæ was about the same for all ages, but that children of ages 1 to 10 years were most liable to severe mental after-effects: Purser[20], Riddoch[6], and Auden[2] also state that a large proportion of their cases were children and adolescents.

The variability of these after-effects suggests that encephalitis lethargica may disturb any mental function. It is, however, possible that, on account of the absence of objective standard methods of investigating mental characteristics, some of the differences recorded in the literature are due to differences of personal opinion. It is very easy to reach the conviction that a patient's memory is impaired, but when another equally competent observer is just as certain that it is unimpaired—a by no means infrequent occurrence—it is necessary to abandon random casual observation in favour of more careful, precise and systematic observation; further, in order to reach the essential facts, one must guard against basing general conclusions on a small number of cases.

In the examination of mental traits we are still far from the exactness and objectivity which marks the work of the physicist and the chemist, but recently some advance has been made and it is desirable that this progress should show itself in observations on the memory, intelligence, emotional disposition, etc., of patients whose ailments are being subjected to scientific examination. The results of tests like the well-known intelligence tests have an objectivity which is lacking in the opinions of casual observers, however shrewd they may be. These tests consist of a miscellaneous collection of exercises which require for their performance knowledge and

skill that a normal child in a normal environment acquires in fairly well-marked stages, such as writing, reading, and giving the meanings of words. Repeated testing has shown which of these are performed successfully by children of different ages, and they have been arranged roughly in order of difficulty. A child of n years who passes the tests which are passed by average children of x years is said to have a mental age (M.A.) of x years, and, as a bright child reaches mental age x sooner than a dull child, and as the results of these tests have been found to be correlated closely with the most reliable estimates of intelligence, he is said to have an intelligence quotient (I.Q.) or mental ratio (M.R.) of $\frac{100\,x}{n}$

These tests have been used in the investigation of the after-effects of encephalitis lethargica, but casually and apparently with some diffidence. Leahy and Sands[17] give the M.Rs. of two of their patients, Hohman[15] of one, Beverley and Sherman[3] of two; Shrubsall[4] mentions two M.Rs. and an M.A. (without the physical age); Kwindt[16] appears to have topped the list, for he applied standard tests to 13 young patients and found six of them normal, four one year behind, and three two years behind.*

II.—Aim and Procedure.

The purpose of this paper is to record the results of an inquiry into the after-effects of encephalitis lethargica on the intelligence of children as shown by the application of mental tests. The number of cases is not so great nor is the investigation so wide or so detailed as could be wished, but the results seem to be of sufficient interest to merit publication. The investigation forms part of a larger inquiry into the intelligence of sick children which was begun by the late Dr. H. J. Watt for the Medical Research Council under the direction of Professor Leonard Findlay, The Royal Hospital for Sick Children, Glasgow; 1,020 patients in this hospital, mostly children of the labouring and artisan classes, have been tested individually.

The tests used were those of Binet as translated by Burt[5]. They are by no means perfect, but they are well-known and generally accepted, and have been well standardised. Most of them were given by the same observer (J. C. M. C.), which is an advantage, for it practically guarantees uniformity of procedure. They were given usually just before the child was to be dismissed from hospital, and was well enough to be sent home; they were never given in the acute stage. All the tests were given in hospital, in the absence of the parents, and under conditions of absolute quietness and privacy. Four doubtful cases were excluded, leaving 46 which were definitely diagnosed as encephalitis lethargica; of these 29 were tested twice, and of these again eight were tested three times.

* Since this was sent to the Press we have seen in *The Psychological Clinic*, Philadelphia, May-June, 1925, XVI (5 and 6), 166-192, a very interesting paper by Miss D. K. Hallowell, entitled "Twenty-four cases of acute epidemic encephalitis," in which are described the results of applying Binet and other tests to 24 encephalitic patients.

It may be suggested that motor disturbances will seriously affect the results of the tests by slowing down the patient's responses, for Binet set time-limits to some of them. In order to meet this difficulty the time was extended somewhat, when delay seemed to be due to this cause. As a time-limit may increase the difficulty of a test, the only effect of this extension is to raise the mental age of the patient and so improve his estimated intellectual status (which, as we shall see, merely strengthens the conclusions to be drawn from our records). The impression made on the experimenters was that motor disturbances were no handicap, an impression which was confirmed later by a comparison of the cases showing the Parkinsonian syndrome with the others (*see* p. 366). No other modification was made in the standard procedure.

There is another possible criticism. The success of the Binet tests depends largely on the assumption that a normal child in a normal environment will at a given age reach a certain stage of mental development, and that if a child reaches this stage earlier (or later) than the average child, it is because he is of superior (or inferior) intelligence. If the environment be abnormal, *e.g.*, one in which the child is not allowed to read, to count, or to use money, the results of the tests are so far fallacious. Now, it may be objected that a child suffering from the after-effects of encephalitis lethargica will not have the same opportunities as his healthy neighbours, and so his intelligence will be under-rated. This criticism is not so serious as may at first sight appear, for the patients have all the opportunities of a normal life: they go to school, they run about at home and in the streets, go messages, and generally do as other children do; they receive every encouragement from their parents and fellows to return to normality.

III.—Observations and Conclusions.

The most convincing evidence of the effect of encephalitis lethargica on the intelligence of children would be provided by tests applied before and after the onset of the illness, but as, for obvious reasons, these must always be rare, and as none of our patients were tested before their illness, we are compelled to collect what information we can from an analysis of the records at our disposal. In making this analysis we shall follow several lines of inquiry. We shall compare (1) the mental ratios of the encephalitic cases with those of the remaining 974 children tested in the hospital, (2) the mental ratios of patients whose illness at the time of the first test was of less than 12 months' duration with those of the other patients, (3) the first and second M.Rs. of patients who were tested twice, (4) the M.Rs. of the encephalitic patients with those of their own brothers and sisters, (5) the M.Rs. of the patients who show the Parkinsonian syndrome with those of the remaining patients, and (6) the M.Rs. of those showing moral and emotional disturbances with those of the other patients.

(1) *M.Rs. of encephalitic and other patients.*

The mean mental ratio of our 46 encephalitic cases at their first test, which was performed at intervals ranging from a few days to five years after the onset of the illness, was 84·63 (*P.E. ±1·24). The mean mental ratio of the other 974 non-encephalitic hospital children who were tested was 90·53 (P.E. ±0·32). The difference between these means is 5·90, and the probable error of this difference is ±1·28. Whence it follows that the odds against this difference being due to chance are over 500 to 1: in other words, if we took at random a sample of 46 cases out of the total 974, the chances against the mean of these cases differing from the mean of all the cases by ±5·90 or more are over 500 to 1[19]. As our 46 cases differ from the rest, so far as we know, only in being cases of encephalitis lethargica, these figures not only show that, at the time of testing, these patients were of lower intelligence than the rest of the hospital population, but suggest a causal relationship between this disease and diminishing intelligence. If the illness did not produce the deterioration of intelligence, then either we must believe that this is the one chance in five hundred, or we must accept the remote possibility that the encephalitics were of lower intelligence before their illness and that this disease attacks most readily those of meaner intelligence.

(2) *M.Rs. of cases of long and cases of short duration.*

Our 46 cases fall into two numerically equal groups: in 23 of them the interval between the onset of the illness and the performance of the first test was less than 12 months; in the remaining 23 it ranged from 12 months to five years four months. The mean mental ratio of the first group is 89·48 (P.E. ±1·75); the mean of the M.Rs. of the second group is 79·78 (P.E. ±1·46). The difference between these means is 9·70, and the probable error of this difference is ±2·28, whence it follows that the odds against this difference being due to chance are over 200 to 1. As the outstanding difference between the two groups is in respect of the duration of the illness at the time of the test, we have here strong confirmation of the suggestion made in the last paragraph that encephalitis lethargica adversely affects the intelligence of children.

(3) *Re-tests.*

The indications given by the above lines of inquiry receive further confirmation from a comparison of the mental ratios of the same patient at different periods after the onset of his illness. Thirty of our cases were tested twice at intervals ranging from 7 to 36 months. The results of these re-tests are recorded in Table I:—

*P.E. = Probable Error of the Mean.

TABLE I.

Patient	(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)
R.D.	87	36	-13	31	-44	-33	2:6	-0·42
A.J.	71	35	- 4	25	-29	-17	3:0	-0·16
D.M.	80	35	18	28	-10	- 5	3:10	0·64
C.H.	80	34	23	27	- 4	- 1	4:2	0·85
C.R.	77	32	3	24	-21	-15	2:1	0·14
S.C.	97	32	- 2	31	-33	-19	2:1	-0·06
C.E.	81	31	0	25	-25	-14	1:0	0·00
M.A.	110	31	- 3	34	-37	-28	0:1	-0·09
S.J.	79	31	19	24	- 5	- 5	0:1	0·78
S.A.	69	30	- 1	21	-22	-11	2:6	-0·05
M.J.	100	29	16	29	-13	-13	0:3	0·55
M.H.	71	28	16	20	4	- 6	0:6	0·79
C.G.	98	26	- 4	25	-29	36	0:0	-0·16
C.P.	91	25	1	23	-22	-17	2:8	0·02
S.H.	82	25	9	20	-11	- 9	0:6	0·44
G.T.	97	24	2	23	-21	-16	0:1	0·07
W.A.	91	24	13	22	- 9	-15	0:0	0·58
D.H.	98	20	2	20	-18	-11	0:9	0·12
S.R.	89	18	7	16	- 9	- 6	0:0	0·42
W.T.	75	13	17	10	7	7	5:0	1·74
M.N.	75	13	- 4	10	-14	-13	0:0	-0·41
O.J.	99	12	12	12	0	0	0·3	1·01
C A.	85	11	- 1	9	-10	- 7	0:0	-0·15
S.N.	110	10	- 8	11	-19	-13	0:3	-0·73
F.F.	97	9	3	9	- 6	-11	0:5	0·34
R.W.	109	9	- 8	10	-18	-15	0:7	-0·82
G.J.	103	9	2	9	- 7	- 6	1:6	0·22
M.B.	78	8	1	6	- 5	- 6	0:3	0·16
P.J.	73	7	2	5	- 3	- 6	2:3	0·47
M.P.	80	7	4	6	- 2	- 1	1:6	0·71

Column (1): M.R. at first test.
,, (2): time between the two tests (in months).
,, (3): rise in mental age (in months).
,, (4): expected rise in M.A. with normal development, *i.e.*, (2) × M.R./100.
,, (5): rise above expected level of normal development, *i.e.*, (3) — (4) (in months).
,, (6): increase in M.R.
,, (7): time between onset and first test (in years and months).
,, (8): index of development, *i.e.*, (3)/(4).
In column (7) intervals less than a month are recorded 0 :0

The mean of all the mental ratios at the first test is 87·73 (P.E. ±1·50); the mean of the M.Rs. of the same 30 patients at their second test is 76·13

(P.E. ±1·50). The difference between these means is 11·60, and its probable error is ±2·12; whence it follows that the odds against the difference being due to chance are over 4,000 to 1. This is still stronger evidence of the effect of encephalitis lethargica on the intelligence of children.

An examination of the Table yields more detailed information on this subject. The first three columns of the Table show the mental ratio of each patient at his first test, the interval (in months) between the first and second tests, and the rise in his mental age (also in months) at his second test. As the mental age marks the level of mental development reached by the patient, it is obvious from Column (3) that in ten cases there is actual retrogression, but of such slight degree that it amounts practically to stagnation, and that in the remaining 20 cases there is some progress, but in 12 of these it is so small that it is almost negligible. The true meaning of these figures is brought out in the succeeding columns.

The significance of an increase or decrease of mental age depends both on the length of the interval between the tests and on the actual magnitude of the initial mental ratio. An example will make this clear. Suppose two children with MRs. 75 and 100 to be re-tested after a year, and suppose that the mental age of each rises by nine months; then the first child is developing normally, for the increase in his M.A. in 12 months should be 75% of 12, which is nine; the other child is actually developing more slowly than he ought, for, as his M.R. was 100, his M.A. should in 12 months increase 100% of 12; he has, in fact, fallen three months below the level of normal development.

We are assuming here that the M.R. of a child remains approximately constant, *i.e.*, that his mental age increases proportionately with his chronological age, or that $\frac{\text{M.A.}}{\text{C.A.}}$ =a constant. This assumption appears to be on the whole correct: the M.R. does fluctuate slightly, but not sufficiently to invalidate the general argument, *cf.* (22) (11). In his "Intelligence of School Children "(22) Terman has given the M.Rs. of 428 children who were tested twice. The tests used appear to have varied somewhat, which is not surprising as they extended over five years and were made by 33 different examiners. For the purpose of comparing Terman's figures with ours we have calculated from his Table 26 (p. 143) the means of the first and second tests. They are: mean of the first test 104·170 (P.E. ±0·712); mean of the second tests 105·397 (P.E. ±0·729). The difference between these means is 1·227, and its probable error is almost as large, viz., ±1·019. Hence there is no significant difference between the means of his first and of his second tests.

Making this assumption, then, we can calculate the mental age that a child of given M.R. should reach after a given interval. These values for our cases are shown in Column (4) of the Table. Column (5) gives the actual rise above the expected level of normal development: in every case but two it is negative. There was then in 44 of our 46 cases a drop in the normal rate of development. This is shown in another way in Column (6) which gives the actual increase in M.R.

The figures in Column (8) give a measure of the rate of development and so provide a method of comparing the various cases at a glance. They are the ratios of actual rise in M.A. (shown in Column (3)) to the expected rise with normal development (given in Column (4)). If the actual rise in M.A. be equal to the expected rise, the figure appearing in this column is 1; if there be no increase, it is 0, while if there be retrogression, it is a negative quantity. Of the 30 cases there are only five in which this figure is above +0·75. Two cases are normal, three more are nearly so, two are serious cases of retrogression; the remaining 23 are characterised by seriously retarded or completely arrested development.

The number of cases is small for the calculation of correlations, but it is suggestive that the correlation between (2), the interval between the tests, and (5), the rise above the expected level of normal development, is significant: it is measured by the correlation coefficient −0·55 (P.E. ±0·08); in other words, the amount of retardation varies with the time between the tests.

With such a dismal picture before us it is gratifying to find that four of the five cases in which the index of development (given in Column (8)) is above +0·75 are of fairly long standing, namely, six years one month, 7:0 years, 2:8 years and 2:10 years at the time of the second test: in the fifth case the illness had lasted 1:3 years at the time of the second test. This suggests that, while arrested development is characteristic of most of our cases during the years following the onset of the illness, yet a few of the older cases show signs of a return to the normal (four of the 14 whose illness was of more than 30 months' duration). This encouraging suggestion receives some corroboration from the results of a third set of tests.

Eight of the patients were tested three times. Their M.Rs., chronological age, and the time between onset and test are shown in the following Table:—

TABLE II.

	First Test			Second Test			Third Test			Fourth Test		
Patient	1	2	3	1	2	3	1	2	3	1	2	3
A.J.	71	3:0	10:9	54	5:1	13:8	65	6:2	14:9			
C.A.	85	0:0	11:10	78	0:11	12:9	73	2:2	14:0			
F.F.	97	0:5	3:6	86	1:2	4:3	92	2:3	5:4			
M.H.	71	0:6	3:7	65	2:6	5:11	53	3:6	7:0			
P.J.	73	2:3	3:11	67	2:10	4:6	59	4:10	6:6	60	6:1	7:9
R.D.	87	2:6	8:2	54	5:6	11:2	60	6:3	11:11			
S.J.	79	0:1	5:5	74	2:8	8:0	84	3:5	8:9			
S.C.	97	2:0	11:9	78	4:9	14:5	72	6:2	15:10			

Column (1): mental ratio.
,, (2): time between onset and test.
,, (3): chronological age.

Four of these cases (A. J., F. F., R. D., and S. J.) show signs of some improvement in mental development at the third test: another (P. J.) shows a slight improvement at a fourth test; but in three of these five cases the M.R. is so far below the borderline of normality that it is doubtful whether the apparent improvement has any significance. In the other three cases the deterioration continues at the third test.

This arrest of mental development, which is probably the most striking of the generalisations issuing from our observations, has already been noticed in the literature. Saunders-Jacobs[21] remarks of her young patients that "many of them appear to have retained whatever knowledge or skill they had before their illness, but experience great difficulty in learning anything new." Hamel and Merland[13] are of opinion that in their cases "there is arrest of psychic development with loss of power to acquire further knowledge." Herd[14] formed the same impression from his cases.

This arrested development provides an explanation of the disastrous effects of encephalitis lethargica on very young children. Hall[12] remarks that his cases of idiocy were practically limited to infants up to 5 years of age. Paterson and Spence[18] report seven cases of idiocy out of 17 at this age. Collin and Réquin[7], and Ebaugh[9], find mental backwardness of greater or less severity to be typical psychic sequelæ of encephalitis in infants. Shrubsall[4] remarks that "in younger children the rate of mental growth seems to have been seriously retarded and in some of them mental deficiency has followed: this has been most evident in the case of those attacked by encephalitis during pre-school age."

When an attack of encephalitis lethargica stops mental development, the degree of mental impairment it produces will depend on the age of the patient at the time of onset of his illness. Imbecility is a necessary consequence of the arrest of mental development at an early age, for an imbecile is one whose mind remains the mind of an infant, and any child whose mental growth ceases at the age of 3 or 4 must become an imbecile.

Older children show less deterioration because their development is arrested at a higher level: the child of 10 still retains his mental age 10, and so may appear dull, stupid and unable to profit from instruction at school, but he is not reduced to imbecility. A numerical example will make this clear. Suppose three children, of ages 4, 8, and 12 years and M.R. 100, cease to develop mentally, then at the end of three years their M.As. will be still 4, 8, and 12 respectively, but their chronological ages will be 7, 11, and 15, and their M.Rs. 57, 73, and 80; the youngest will be definitely feeble-minded, the second will be on the borderline of deficiency, and the third will be merely dull and backward.

Five of our patients had M.Rs. of not more than 60 at their last test; of these three were less than 5 years old at the onset of their illness: of the 41 with M.Rs. over 60 only seven were then less than 5 years old. Of the

14 with M.Rs. below 71, six were less than 5 years old at the onset of their illness, whereas of the remaining 32 above 70, only five were then of this age. The incidence of mental defect is therefore relatively much higher among the very young than among the older children.

The seriousness of the effects of encephalitis lethargica on the intelligence of children is shown by the fact that of 46 cases 12 (26%) had at their final test mental ratios below 70, while 25 (54%) had M.Rs. below 80. For the normal population the corresponding proportions, calculated from Terman's figures[22], are 3% and 11%; for the other 974 children tested in the hospital (which included several mentally defectives who had been admitted for purposes of observation) they are 6% and 20%.

(4) *M.Rs. of patients' brothers and sisters.*

A final line of inquiry lies in a comparison of the mental ratios of the patients with those of their brothers and sisters. The brothers and sisters of 23 patients were tested in hospital under exactly the same conditions as the sick children. They numbered 27, for in four families we were able to test two healthy children. We selected as far as possible those who were nearest in age to the patients.

The mean M.R. of these 27 brothers and sisters was 96·00 (P.E. $\pm$1·35); the mean M.R. of the patients at their first test was 85·61 (P.E. $\pm$1·77); at their second test it was 76·40 (P.E. $\pm$1·80: there were 20 cases). The difference between 96·00 and 85·61 is 10·39; its probable error is $\pm$2·23: hence it is quite significant. The difference between 96·00 and 76·40, *i.e.*, 19·60, is much more so.

Although children in the same family do vary in intelligence it is, therefore, highly improbable that the above difference is a matter of chance. In eight cases the mother of the patient volunteered a comparison between the children, and in six of these it was the patient who was said to have been cleverer or brighter than the other. Such judgments are not of much value, but they support the conclusion that the difference between the intelligence of the patients and that of their brothers and sisters is the result of the illness.

All these lines of inquiry, then, point in the same direction: they indicate that, while in a few cases encephalitis lethargica leaves no serious intellectual after-effects, yet it does on the whole arrest or retard mental development to such an extent that it appreciably reduces the intelligence of the patients, and that the deterioration is greatest in young children, amounting sometimes to imbecility. The importance of this conclusion can hardly be over-estimated, for we are here in presence of mental defect which is not innate: children, apparently sound and developing normally in mind and body have by disease suffered intellectual deterioration in some cases sufficiently grave to necessitate institutional care. Whatever may be our views on innate capacities, we have to acknowledge that by a misfortune of circumstance the growth of these capacities may be arrested or retarded with disastrous effects on mind as well as on body.

It remains to consider this deterioration in relation to the Parkinsonian syndrome and to disturbances of character.

(5) *M.Rs. of patients with the Parkinsonian syndrome.*

Sixteen of our patients developed the Parkinsonian syndrome: it was, therefore, possible to compare their intelligence with that of the others. Their mean M.R. at the first test was 84·90 (P.E. ±2·0), that of the remaining 30 patients was 84·47 (P.E. ±1·58). The difference between these averages is 0·43, and its probable error is ±2·54: there was, therefore, no significant difference between the two groups at their first test.

In six of the cases the syndrome had not clearly developed at the time of the first test: it seems, therefore, more satisfactory to compare the results of the final tests on the two groups, for the syndrome had then developed in all cases. The mean M.R. of the Parkinsonian group at the final test is 80·56 (P.E. ±1·74), while that of the other patients is 75·27 (P.E. ±1·50). The mean of the first group is 5·29 higher than that of the second, but, as the probable error of this difference is 2·30, it is not statistically significant. An examination of the "development ratios" of those who were tested twice gives the same result. Our figures, then, show no significant difference between the intelligence of those who have and those who have not the Parkinsonian syndrome.

It should be remarked that this means only that our observations have failed to show a significant difference: it is still possible that more extensive testing might reveal such a difference. In any case it is clear that our estimates of the intelligence of the Parkinsonian patients do not appear to have been adversely affected by slowness of motor response.

(6) *Defective intelligence and moral disturbance.*

Among the most apparent and most distressing of the mental after-effects of encephalitis lethargica is a change of character and emotional disposition which may vary in degree from a slight intensification of emotionality to maniacal outbursts, from paltry peccadillos to serious criminal offences. Quarrelsomeness, violence, destructiveness, cruelty (especially to younger children), fits of anger, irritability, vicious temper, rage, biting, scratching, screaming, obstinacy, and general unmanageableness are common, as are also stealing, swearing and lying. In some cases there is merely heightened emotionality, shown in immoderate laughing and crying and in general excitability and noisiness. Along with all these disturbances there often goes friendly, affectionate, pleasant good nature. The outbursts frequently seem to be compulsive, *i.e.*, due to some inner urge, but they appear to be somewhat controllable, for they vary with the patient's social environment: a child who is comparatively docile in hospital is sometimes unmanageable at home.

Of our 46 cases 29 showed some sign of emotional or moral disturbance: the remaining 17 appeared to have suffered no change in character or disposition. Comparison of these two groups fails to show any significant difference in mental ratio. The average M.R. of the first (emotionally or morally unstable) group is 84·24 (P.E. ±1·56); that of the other (emotionally and morally normal) group is 84·82 (P.E. ±2·20): the difference between these means is only 0·58, while its probable error is ±2·70, so that it is not significant. Hence, whatever may be the ultimate explanation of the moral and emotional instability, it does not appear to be due to intellectual deterioration.

Nor do our observations lend any support to the generalisation that "moral imbeciles do not suffer from severe mental defect, while those suffering from severely impaired intelligence do not present psychical and emotional disturbances in any marked degree "[1], or that "the younger children tend to suffer mental impairment rather than moral perversion, while older children show a tendency in the opposite direction "[1]. Moral and emotional disturbance is present in children of all ages; four of the five of our patients who were below 5 years of age at their first test were suffering in this way.

IV.—Summary.

1. The average intelligence of 46 children suffering from the after-effects of encephalitis lethargica was significantly lower than that of 974 other hospital patients and of their own brothers and sisters.

2. The mean intelligence of those whose illness had lasted over 12 months was significantly lower than that of the patients whose illness was of shorter duration.

3. The average intelligence of 30 of these patients who were re-tested after intervals varying from 7 to 36 months showed a significant deterioration at the second test.

4. This deterioration appears to be due to arrested mental development.

5. The arrest of development is most serious in very young children.

6. There is definite statistical evidence that encephalitis lethargica does produce intellectual deterioration (as measured by the mental ratio), which may amount to mental defect, in some children, but not in all, who before their illness were presumably normal.

7. Post-encephalitic children with the Parkinsonian syndrome showed a deterioration in intelligence not significantly different from that of the other patients.

8. There was no significant difference between the intelligence of the 29 patients showing disturbances of character and emotionality and that of the remaining 17.

We desire to acknowledge our indebtedness to the Medical Research Council for financial help in this work, to Professor Leonard Findlay for his unremitting and invaluable assistance, and to Dr. M. M. Stevenson for supplying information about the patients who showed the Parkinsonian syndrome.

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THE RELATION OF HYPERTELORISM TO MONGOLISM;

With Description of a Case.

BY

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Since D. M. Greig[1] first described the cranial deformity called by him ocular hypertelorism seven other cases have been recorded. The two most recent are those of F. M. B. Allen[2] and W. B. Drummond[3]. The most salient and constant feature recognisable clinically is the great breadth between the eyes. Other characteristic signs are mental deficiency (present in eight of nine cases), brachycephaly, the presence of a median groove in the frontal bone, and depression of the bridge of the nose.

The following case, although not very marked, shows some interesting points:—

G. L., girl, aged 15 months, was brought up to the out-patient department for backwardness. She could not stand, talk, nor feed herself, and she made no attempt to play with toys. The parents were healthy, and had had one other normal child.

The striking points about the appearance of the child were the widely separated eyes, the flat face, and the receding chin. The distance between the inner canthi was 1·2 ins., and that between the pupils 2 ins. The orbital height was 1·25 ins., the orbital width 1·5 ins.; the orbital index was therefore 83·3 or microseme. The eyelids were thick, and the lower lids everted.

The skull was flattened behind and looked brachycephalic. However, the length was 6·4 ins., the breadth 5 ins., and the cephalic index 76·9, or mesatocephalic. The circumference of the head was 18·75 ins., the frontal eminences were prominent, and there was a vertical groove running down the middle of the frontal bone. The hairy scalp showed a V-shaped peak in the middle line. The anterior fontanelle was widely open, the length being 2·5 ins., and the breadth 2·6 ins. The ears were large and stood out from the side of the head. The bridge of the nose was depressed, and the nose itself small. The length of the face was 3·3 ins., and the breadth 4·5 ins. The tongue was apparently normal. The palate was highly arched, and the child was a mouth breather. Eight teeth were present, the central and lateral incisors. They had appeared at the eighth month.

The fingers were thin and tapering, and the little finger was normal. The toes were similarly shaped to the fingers, but the gap between the hallux and the second toe was considerably greater than that between the other toes. There was slight cyanosis of the feet. The abdomen was prominent, and there was a large umbilical hernia. Muscle tone was markedly deficient; the child could put her head between her heels like a case of amyotonia congenita.

The costochondral junctions were enlarged, and there was a rickety kyphosis of the dorsal and lumbar spine. A skiagraph of the wrists showed marked rickety changes.

Hearing and sight were apparently normal. The fundi oculorum showed no abnormality.

A skiagram of the skull showed that the clinoid processes were rather close together, and that the sella turcica was a little on the shallow side. "It is probably not justifiable to assume that this is beyond the limits of the normal." (Dr. A. E. Payne.) The blood sugar three hours after a meal was 0·07%.

In this case there are certain peculiarities which are usually associated with mongolian deficiency. Perhaps the most striking is the abnormal gap between the hallux and the second toes. In addition there is mental dulness, amyotonia, flatness of the face, depression of the bridge of the nose, smallness of the nose, flattening of the occiput, projecting ears, widely open fontanelle, and a highly arched palate.

Study of the previously published cases shows that many of them had characteristics usually associated with mongolism. Thus, Greig's first case had a flat nose and a fissured tongue. Also she was strikingly fond of music, which is very characteristic of mongolism. She had tubercular adenitis of the neck, and died of pulmonary tuberculosis.

His second case had a depressed nasal bridge, an oblique right palpebral fissure, a flattened occiput, a highly arched palate, and the little fingers were disproportionately small. She also had tubercular adenitis of the neck, and died of spinal caries.

Muir's[4] case showed a highly arched palate, flattening of the occiput, and large ears. This case also showed flattening of the pituitary fossa by radiography.

Of Cockayne's[5] two cases, the first showed flattening of the occiput, while the second, a boy, had only one small testicle in the scrotum. In addition his fingers were short and square, and there was dwarfing of the big toe.

Drummond's case showed flattening of the bridge of the nose, a high and narrow palate, a fissured tongue, while her hands " reminded one of those of a mongol."

Allen's patient, also a boy, was a cryptorchid. His palate was high and arched, and the bridge of the nose was depressed.

No doubt most of the bony peculiarities are due to the malformation of the sphenoid which, according to Greig, is the primary lesion in these cases. But even so, the presence of so many common characters is suggestive that the pathology of the two conditions overlap, and that an explanation of one would help considerably in the understanding of the other.

In this connection it is interesting to note that both the male patients suffering from hypertelorism were cryptorchids. Jodiche[6] studied the serum of mongols by Abderhalden's sero-diagnostic method, and found evidence of degeneration of a number of organs, especially the reproductive glands. That the reproductive glands are not always affected in hypertelorism is, however, suggested by the normal sexual development and menstrual function of Greig's first case.

If there is a common lesion in mongolism and hypertelorism, it seems most likely to be in the pituitary gland. A deformed sphenoid might conceivably be either the cause or the result of dyspituitarism, and this would explain the disturbance of growth and infantilism.

The idea that the pituitary is to blame in mongolian deficiency is no new one. Schüller[7] in 1907 pointed out that mongolism was in many respects the direct opposite of acromegaly, and suggested that the condition might be called " acromicry." He also called attention to the frequency of cryptorchidism in this affection. Timme[8] found an excavation under the anterior clinoid processes communicating with the sella turcica in 23 out of 24 cases of mongolism, which was not present in normal children. Clift[9] working with a larger number of cases, was unable to confirm this. He found that the condition was just as common in normal children, but his work by no means put the pituitary out of court, as he observed that normally the anterior clinoid processes are widely separated, and can only be involved in such extraordinary enlargement of the pituitary body as is found in tumours.

Of the other theories of mongolism, that of Stœlztner [10] is interesting. He regards it as a result of thyroid exhaustion of the mother during pregnancy. He reports three cases of myxœdematous women who became pregnant. In each case the child was born with markedly mongoloid characteristics.

While it is not suggested that either hypertelorism or mongolian deficiency is due to a primary lesion of the pituitary body, it does not seem unlikely that some secondary affection of this gland is responsible for those phenomena common to both conditions.

SUMMARY.

1. A mild case of hypertelorism is reported.

2. The presence of characteristics usually associated with mongolism in this and other cases is discussed.

3. It is suggested that dyspituitarism is a lesion common to the two conditions.

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